We are excited to welcome you to the sixth volume of the Stanford Journal of Public Health, which—for the first time—features voices from not just the public health community at Stanford, but from across the nation.

The current U.S. administration has aroused deep uncertainty in the public health community, clouding the future of public and global health with numerous policy priorities: the attempts to repeal and replace the Affordable Care Act, attacks on climate change initiatives, and a far-reaching national budget that would slash global health funding. Now more than ever, the Journal seeks to encourage and uplift scholarly discourse on today’s most pressing public health topics and to organize and center the student public health community’s stories and discoveries.

In this issue, we invite you to explore the expansive reach of public health issues. Learn about humor therapy in medicine, discover how our writers developed a rapid and inexpensive biosensor, enter a conversation about recent healthcare reform regarding end-stage renal disease, and digest a comparative analysis of health systems. Immerse yourself in our writers’ worlds through their vivid and moving storytelling, from a researcher’s journey uncovering humanity by mapping diseases to a student’s moving account of his brother’s fight with cancer.

Since the Journal’s founding in 2011, we have been fortunate enough to work with inspiring faculty and staff from all corners of campus, and we would like to especially thank The Program in Human Biology and Students Activities and Leadership for their continued generous support of our endeavors. And finally, we want to thank our talented and dedicated staff for making all of this possible.

We celebrate the diverse perspectives of our student public health community, and we hope you’re just as encouraged and inspired by these voices as we were when we read them. As always, we welcome your thoughts, comments, discussions, and suggestions about our work, the public health community, or any issue you would like to see us cover.

Please don’t hesitate to reach out to us at stanfordjournalofpublichealth@gmail.com.

Sincerely,
Aprotim C. Bhowmik ’18
Jason Li ’18
Michelle Bach ’19
**THE EDITORS**

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Michelle Bach is a sophomore interested in Global Health and infectious disease. Michelle is currently conducting research on Cystic Fibrosis at Stanford Medical School, and she has previous research experience in oncology and bioengineering. Michelle is currently involved with Pacific Free Clinic, is a licensed Emergency Medical Technician, and is a Certified Nursing Assistant (CNA). Serving as a co-editor-in-chief has been a rewarding learning experience! She has learned about the current discourse on public health topics and research, and she hopes to share her knowledge of these topics with others!

**LAYOUT EDITOR**

Lillian Liao is a senior majoring in biology and music, with plans to complete a Master’s in Epidemiology and Clinical Research at Stanford. She is interested in becoming a physician and providing patients with quality one-on-one care, but is also passionate about having a broader, population-based perspective on health. Last spring, Lillian completed a tutorial in public health at the Oxford School of Public Health. She has been researching colorectal cancer for the past year in Calvin Kuo’s lab at the Stanford School of Medicine, and will be working with Dr. Latha Palaniappan’s lab this upcoming summer to investigate mortality and socioeconomic differences between diverse Asian American racial/ethnic subgroups in the U.S. She also serves as a preclinical volunteer and Mandarin interpreter at the Pacific Free Clinic. As layout editor, Lillian has enjoyed reading the wonderfully written pieces to be included in the journal and gaining new insight into public health; she hopes you do too!
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The policy section explores the intersection of public health research and innovation and its deployment in the real world. The section approaches health topics at the forefront of scientific debate by integrating legislative, ethical, and economic perspectives.
Introduction

In recent years, scientific research in genetics and cellular mechanisms has led to a new approach to the study of biology—one that encourages researchers to be innovators and agents of change rather than simply observers. This burgeoning field—called synthetic biology—focuses on the creation of medical technologies and artificially engineered life by manipulating the natural order of living entities. In other words, synthetic biology is geared towards changing the existing forms of life (usually on a genetic basis) to develop insights regarding health and medicine. Although this field is producing groundbreaking discoveries, research in synthetic biology is being partially tempered by a new brand of ethics. Because synthetic biology relies on the ability to change current living entities, it inevitably raises ethical concerns regarding the potential consequences of engineered life. Common ethical dilemmas surrounding synthetic biology include the idea of “playing God” when manipulating life or using a reductionist perspective to lower the “dignity” of life so as to treat genetic information as a mere toolkit (Heavey, 2013). The strongest ethical concern deals with the possibility of adversely impacting human health, degrading the environment, or facilitating the practice of bioterrorism. These potential misapplications of synthetic biology are collectively referred to as dual-use research of concern (DURC) (Cho & Relman, 2010; Edwards, 2014). Especially due to the horrific attack during 9/11 and the subsequent rise in the potential for bioterrorism, dual-use has become an increasingly important ethical issue in determining when to permit synthetic biology research. However, in the process of conducting ethical examinations of research, we must ensure that the rights of scientists and research institutions are not infringed upon. Furthermore, we must consider the potential benefits of synthetic biology research in the face of possible harms due to dual-use. In this paper, I assert that synthetic biology research should be treated largely with a policy of openness and acceptance—but at the same time, should be subject to reasonable regulations and ethical examinations by appropriate governing bodies. This practice will allow synthetic biology to flourish while also regulating the research to prevent dual-use harms.

Basics of Dual-Research of Concern (DURC)

One of the landmark events that spurred the development of new ethical concerns regarding dual-use was the creation of a synthetic genome that could replicate itself in bacterial cells (Garrett, 2013; PCSBI, 2010). Conducted by the J. Craig Venter Institute, this research project caused much controversy over synthetic biology, as possible mistakes could have led to an outbreak of bacterial cells that harm human health or degrade the environment. Additionally, if the methodology of this research project were easily reproducible, terrorist organizations might be able to use Venter’s publications for bioweaponry. Thus, in response to the creation of this synthetic genome, a new brand of ethics regarding dual-use was born. The U.S. National Science Advisory Board for Biosafety (NSABB) defines dual-use as “research that … can be reasonably anticipated to provide knowledge, products, or technologies that could pose a threat to public health, agriculture, plants, animals, the environment, or materiel” (Cho & Relman, 2010). This definition is quite broad by design, as many of the potential consequences of synthetic biology are unknown—simply because the field is still in its infancy. However, it is relatively clear among ethicists that research in synthetic biology is moving faster than the development of germane ethical examinations/regulations (Biller-Adorno et al., 2013; Edwards, 2014; Heavey, 2015). This “lag time” increases the possibility of harms due to dual-use being realized before appropriate policies are promulgated. As such, a central issue in synthetic biology is reconciling ethical policies with current research—but this act of reconciliation sparks questions about the extent of re-
strictions that should be put in place to avoid harms due to dual-use while not stifling scientific research.

**Value of Openness in Synthetic Biology**

Throughout the history of scientific research, it has been well-established that discovery and innovation are best promoted using a policy of openness, in which information and methodologies are widely shared and reproduced (Cho & Relman, 2010; PCSBI, 2010; Smith, 2013). This principle holds for the field of synthetic biology as well, as it is a branch of science research like any other. Therefore, in order to maximize the utility of synthetic biology research, it is necessary to keep the field as open and unrestricted as possible. This approach is often referred to as a laissez-faire policy regarding synthetic biology (Smith, 2013). When continuing this utilitarian mode of analysis, however, we reach a stumbling block: the quantification of the possible harms of dual-use.

Ethicists have found it difficult to estimate the potential harms, largely because dual-use is intrinsically a speculative enterprise. In other words, quantifying the harms due to dual-use would be relatively inaccurate, as it is possible that very few or very many of the harms will actually materialize. Furthermore, the potential harms themselves are difficult to estimate, as they can range from being almost innocuous to being catastrophic (Edwards, 2014; Smith, 2013). For example, disease outbreaks due to safety breaches in research labs could be trivial if the disease is weak or if there are vaccines/cures for distribution, whereas the outbreaks could be devastating if there are no protective measures in place. Thus, the range of possibilities is too broad for sufficiently accurate quantifications of the risks of dual-use.

A common solution to this ethical dilemma is to combine the utilitarian value of openness with a deontological argument regarding intellectual freedom (PCSBI, 2010). The idea of intellectual freedom stems from the fundamental belief that we, as people, have the right to think about and investigate any issues that we want. In the case of dual-use, intellectual freedom is more specifically defined as the right of scientists and research institutions to pursue any scientific investigations that they wish. However, both of these definitions have a relevant caveat: the pursued investigations as a result of intellectual freedom must not produce unethical consequences. In other words, in the case of dual-use, while practicing intellectual freedom and potentially increasing utility, scientists and research institutions must ensure that they are not harming human health, degrading the environment, or increasing the likelihood of bioterrorism. This idea of intellectual freedom was used by the Presidential Commission for the Study of Bioethical Issues (PCSBI) when analyzing the ethical nature of the synthetic genome created by the J. Craig Venter Institute (PCSBI, 2010). The PCSBI employed the concept of intellectual freedom to introduce the useful corollary of regulatory parsimony, which suggests that synthetic biology should be subject to “only as much oversight as is truly necessary to ensure justice, fairness, security, and safety while pursuing the public good” (PCSBI, 2010).

It is clear from the PCSBI’s concept of regulatory parsimony that synthetic biology is most effective when in an environment of openness. To excessively restrict synthetic biology research would be to take away the right of scientists and research institutions to intellectual freedom. Thus, the value of openness in synthetic biology is both scientifically supported and ethically valid. However, ethicists and the PCSBI promote intellectual freedom and regulatory parsimony with the assumption that there will be necessary restrictions in place to prevent the harms of dual-use. This balanced approach attempts to grant as much openness as possible while still adding necessary regulations to preclude the risks of synthetic biology research from being realized.

**Ethical Basis of Regulations and Policy Implications**

Before discussing the regulatory policies that would be ethical to implement in synthetic biology research, it is worth investigating why regulation is ethical in the first place. It has already been established that intellectual freedom is a right that scientists and research institutions should possess. Without a significant amount of independence and self-motivation, progress in research would be greatly hampered (Cho & Relman, 2010; PCSBI, 2010; Smith, 2013). However, scientists and research institutions must not use their freedom to purposefully or inadvertently contribute to unethical consequences regarding dual-use. It is within reason to
consider that labs in the United States and around the world can make mistakes (or do intentional harm) that hurts human health, degrades the environment, or promotes bioterrorism. In all of these cases, it would be unethical to allow such research because the consequences can be harmful to our society. Thus, we have an ethical issue to balance—by allowing sufficient intellectual freedom without losing regulatory control (PCSBI, 2010).

In finding an appropriate balance, it is useful to consider the weights of the two sides: intellectual freedom for effective research versus regulation for the prevention of harms due to dual-use. The former (i.e., intellectual freedom) is a constantly applicable right; that is, scientists and research institutions would be definitively reduced in capacity if intellectual freedom were limited. On the other hand, the latter (i.e., regulation to prevent harmful consequences) is largely based on speculation. Regulations would be put in place to prevent potential harms due to dual-use, but there is no definiteness that is associated with those harms. (In other words, the harms may or may not actually be realized.) Therefore, the ethical balance tips in favor of intellectual freedom, and in crafting appropriate policies, we must consider this difference in weight of the two sides.

In light of the higher weight of intellectual freedom, we must ensure that all applicable policies provide sufficient but not excessively stringent regulations on synthetic biology research. A felicitous starting point would be to advocate self-regulation of research by the scientists and institutions themselves (Smith, 2013). This policy can be implemented both informally and formally. In the former case, scientists would simply be subject to their own ethical decision-making and would hopefully use common sense and ethical judgment to choose proper research projects and ample safety measures. This practice is sometimes referred to as upstream engagement, in which scientists are required to consider safety and security threats due to dual-use while, not after, they conduct their research (Edwards, 2014). In the latter case, research institutions would subject their scientists to an ethical review before they embark upon a research project. This would be the first official “line of defense” against any unethical research practices. Both of these aspects of self-regulation are ethically valuable because they limit any reduction in intellectual freedom.

At the same time, since self-regulation has a relatively high risk of bias and corruption, it is necessary for an external governing body to conduct sufficient ethical reviews of synthetic biology research. This aspect of policy is more controversial, as it is difficult to draw boundaries between external regulations that are ethically justified and those that are excessive. However, most ethicists agree on the point that current ethical reviews for synthetic biology research are lacking in rigor (Biller-Adorno et al., 2013; Edwards, 2014; Heavey, 2015). Because the field of synthetic biology is developing so quickly, it is difficult—but necessary—for ethical reviews to maintain the same rate of development. The PCSBI has suggested that research institutions be subject to the NIH Guidelines for Recombinant DNA Research and undergo ethical examinations facilitated by the Federal Bureau of Investigation (FBI) and the Department of Homeland Security (PCSBI, 2010). With regard to international research efforts in synthetic biology, ethicists have suggested using the World Health Organization (WHO) to construct a body of regulations modeled after the Codex Alimentarius, which regulates food safety. Some ethicists have also encouraged researchers to engineer suicide genes in their synthetic biology projects, which would enable the engineered life to be relatively easily killed if deemed uncontrollable (Garrett, 2013). Yet another compelling suggestion is for all research publications to include an ethical assessment—thus ensuring that all scientists and institutions are undergoing proper ethical examinations (Heavey, 2015). All of these suggestions merely brush the surface of a large, developing field in policy regarding synthetic biology. At this point, ethicists and policymakers are fighting an uphill battle, as more regulation is almost certainly necessary to deal with the possible harms due to dual-use. However, in order to encourage progress in synthetic biology, it is critical to ensure that these regulations do not become excessively stringent on the intellectual freedom of scientists and research institutions.

A Glimpse of the Future in Synthetic Biology

As aforementioned, the field of synthetic biology is often touted to be pivotal in the coming years of development in medical technologies and scientific
innovations. One of the main reasons for the excitement about this field is that scientists are using nature’s building blocks of life as the foundation for our own innovations. Nature has been priming its creations for millions of years, so using these naturally primed tools will significantly boost our ability to innovate. For example, scientists have learned that bacteria have Clustered Regularly Interspaced Palindromic Repeats or a CRISPR-Cas system, which functions in bacterial immune response. By synthetically controlling the CRISPR-Cas system using small molecules, scientists have been able to learn about DNA repair mechanisms and genome editing (Yu et al., 2015). Another example of cutting-edge research in this field deals with the synthetic modification of histones and nucleosomes, which are related to chromatin structure and gene expression. By changing the structure of histones and the positioning of nucleosomes, scientists have been able to affect gene silencing and other features of transcription (Keung et al., 2015). Both of these research projects have a wide breadth of applicability, ranging from cancers to stem cell use to neurodegenerative diseases.

This well-defined importance of synthetic biology makes it even more vital to balance the intellectual freedom of scientists and research institutions with the necessary regulations to prevent the harms of dual-use. By doing so, we will not only be ethically justified in giving more weight to intellectual freedom but also be scientifically shrewd in considering the potential benefits of this research. One final note of encouragement is that “the dual-use dilemma that first hit chemistry a century ago, and then hit physics a generation later, is now emerging with special force in contemporary biology” (Garrett, 2013). Thus, the general issue of dual-use is not completely unprecedented and can be resolved over time with proper ethical judgment. With a resolution that provides an appropriate balance of intellectual freedom and regulations, the field of synthetic biology will be primed for innovation.

References


Over the course of the last half century, a significant array of legislative initiatives has been launched to reform America’s healthcare system. Successful reforms, the most significant of which include Medicare’s End Stage Renal Disease Program Amendments, the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, the Health Care and Education Reconciliation Act of 2010, and the Patient Protection and Affordable Care Act of 2010, have been taken to streamline coverage and delivery systems of health care programs. Collectively, these initiatives have helped improve access to kidney transplantation, alleviate costs of dialysis and medications, increase coverage for uninsured patients in the post-transplant stage, and introduce novel healthcare delivery systems for end stage renal disease patients. However, these reforms may also impose potential challenges for organ transplantation (by exacerbating the organ shortage crisis or placing significant financial pressure on transplant centers). The following paper analyzes both the advantages and setbacks of recent healthcare reforms in Medicare, Medicaid, and Accountable Care Organizations in the context of end stage renal disease.

Medicare Reforms

1. A history of payment policies and reforms in Medicare’s dialysis program

Medicare was formally enacted in July 1965 under President Lyndon Johnson, as a national social insurance program for Americans aged 65 or older. Dialysis was developed in the 1960s, but because of its high costs, was unavailable to most kidney failure patients in need of the treatment. Thus, in 1972, Congress passed the End Stage Renal Disease (ESRD) Program into law, setting Medicare as the nation’s primary provider and payer for dialysis treatment in patients with end-stage renal disease. The ESRD program expanded the original Medicare coverage to include all patients (regardless of age) diagnosed with chronic renal failure and insured under Social Security. ESRD patients, who constitute about 0.5% of Medicare’s beneficiary population, contribute to 5% of all Medicare expenditures (Nissenson and Retting, 1999).

Due mostly to the discovery and increasing use of erythropoietin stimulating agents (ESA’s), Medicare spending on dialysis treatment skyrocketed over the last twenty years (Swaminathan et al., 2012). According to Swaminathan et al., “by the beginning of 2005, erythropoietin stimulating agents had become the single largest drug expenditure within the entire Medicare program, with total annual expenditures on the drug for dialysis patients approaching $2 billion.” Healthy kidneys produce normal levels of the erythropoietin hormone, which prompt bone marrow to make red blood cells that carry oxygen throughout the body. However, individuals with kidney failure or chronic kidney disease will often have lower-than-normal levels of erythropoietin, which consequently lead to lowered red blood cell count and extremely elevated risks of developing anemia. ESA’s, though effective at treating anemia in ESRD patients, have stretched Medicare spending to alarming heights.
As the data table from Nissenson et al. indicates, Medicare expenditures increased at an annual rate of about 30.5% from 1974 to 1981. As a result of these costs, Medicare's end-stage renal disease program has undergone several payment policy reforms since its inception.

Initially, Medicare's ESRD program paid dialysis providers using the traditional fee-for-service cost-based reimbursement method (Nissenson and Rettig, 1999). This method paid providers for each provision of dialysis, billable medication, lab test and dialysis-related service, thus providing a powerful incentive to increase volume and intensity of dialysis services (Swaminathan et al., 2012). Medicare first attempted to lower dialysis treatment costs by controlling only the frequency of dialysis, limiting providers to no more than three dialysis sessions per week. However, this reform proved ineffective because it provided no clear monetary cap on reimbursement rates. The Omnibus Budget Reconciliation Act was then introduced in 1981, which added the idea of a composite rate: a fixed rate paid to providers for each dialysis session ($131 per treatment in hospital facilities and $127 per treatment in freestanding facilities), in addition to the previous frequency reform. For the first time, payments for home dialysis treatments, where the equipment, supplies, and support services are provided through a facility, would be made at the same rate as in-facility treatments ($131 or $127) (Laaser et al., 1990). Since home dialysis is less costly than in-facility treatments, the composite rates estimated lower-cost, higher profit home dialysis. However, contrary to predictions, the prevalence of home dialysis didn’t increase substantially (Laaser et al., 1990). Further, these composite rates did not include separately injectable medications (ESA's, Vitamin D, Iron) or separately billable services (laboratory tests), which accounted for 40% of cost for outpatient dialysis services. Thus, Medicare's spending on dialysis continued to surpass projected costs.

Then, in 2003, the Medicare Prescription Drug, Improvement, and Modernization Act (MMA), called for a report by the Secretary of Health and Human Services on a bundled dialysis prospective payment system (PPS) for dialysis treatments. By 2006, sufficient evidence had accumulated on the potential for bundled payments to reduce Medicare dialysis spending. Medicare launched the system of bundling dialysis payments with dialysis-associated diagnostic and treatment care in 2011 (Swaminathan et al., 2012). Bundled payments included costs of dialysis-related oral drugs, injectable medication, and laboratory tests (previously paid for separately) into a single composite rate for ESRD services. In 2015, Medicare paid a base rate of $239.43 per treatment for up to three hemodialysis treatments per week, adjusting the base rate to account for certain factors that affect the cost of a treatment, including costs to stabilize patients and to provide training during the first 4 months of dialysis treatments. Whether this bundled payment system can ultimately help cap the increasing rates of dialysis costs, while also ensuring quality of care, remains to be determined. Centers for Medicare & Medicaid Services implemented its Quality Incentive Program in 2012, which can reduce Medicare payments for dialysis treatments to facilities by up to 2% based on the quality of care provided. Policy makers should continue to work with researchers, and renal provider and patient communities, to ensure that costs of dialysis, health care spending, and legislative regulations are all balanced with patient's quality of care.

II. End Stage Renal Disease Program Amendment of 1978

The ESRD Program Amendments of 1978 also included several provisions to encourage home dialysis and eliminate existing financial disincentives to transplantation. Home dialysis was not only shown to be more cost-efficient, but studies also suggested that patients performing home dialysis may have increased autonomy and health-related quality of life. Reacting to a decrease in the percent of patients dialyzing at home, the Amendments offered full coverage for home dialysis supplies and 100% reimbursement for home dialysis equipment (the Omnibus Budget Reconciliation Act mentioned previously replaced full coverage with composite rates in 1981) (Eggers, 2000). Further, the Amendments eliminated financial disadvantages to transplantation by providing for immediate Medicare entitlement, without the previous three-month waiting period, for patients choosing self-dialysis or transplants from living donors as their initial treatment modality. Further, while the original 1972 ESRD Program limited Medicare entitlement provisions to one year following a successful trans-
plant, these amendments extended Medicare coverage to three years post-transplant (Eggers, 2000). Cumulatively, the 1978 amendments provided for more complete coverage of home dialysis costs, increased coverage of kidney acquisition costs, and implemented incentive reimbursement rates that would assure the most cost-effective delivery of dialysis services.

III. Health Care and Education Reconciliation Act

The Health Care and Education Reconciliation Act, passed in 2010, has significant effects on kidney transplantation: it closed the Medicare Part D (Prescription Drug Coverage) “donut hole,” extended the ban on lifetime limits for insurance, (Title I, Section 2711), prevented rescission of coverage to existing health plans (Title I, Section 2712), and provided a 50% discount on brand-name drugs for Medicare patients beginning in 2011 (Subtitle D, Section 3301). The Medicare “donut hole” refers to a coverage gap—the period of consumer payment for prescription medication costs in-between the initial coverage limit and the catastrophic-coverage threshold. Over a quarter of Medicare Part D participants stop following prescribed drug regimens when they hit the donut hole, according to the U.S. Department of Health (Claffey, 2010). By 2020, the Reconciliation Act states that the federal government will provide up to a 75% discount on brand-name and generic drugs. By creating discounts on medication purchased within the gap range, the Health Care and Education Reconciliation Act has the potential to close the coverage gap until it is eventually eliminated. Kidney transplant patients would thus be able to better afford costs of medication and experience decreased rates of non-compliance due to increased drug affordability.

Medicaid Reforms

Medicaid, the second major health care coverage program in the United States, is a joint federal and state healthcare insurance program for American citizens of all ages with incomes up to 133% of the Federal Poverty Level. Unlike Medicare, Medicaid is financed by a combination of federal, state, and local funds, and is administered primarily by the states. Medicaid has been significantly impacted by the recent Patient Protection and Affordable Care Act reform, as well as by the introduction of an exciting new health care delivery system, Accountable Care Organizations.

I. Patient Protection and Affordable Care Act

The Patient Protection and Affordable Care Act, signed into law on March 23, 2010, introduced a series of changes to the organization and financing of the American healthcare system. By 2023, the Act is estimated to provide health insurance to 24 million previously uninsured Americans. About half of these individuals are projected to receive coverage through expansion of Medicaid, and the other half through new insurance exchanges and expanded employer-based coverage (Axelrod et al., 2010). Medicaid eligibility will be expanded to individuals under 65 years old with income below 133% of the federal poverty level (Axelrod et al., 2010). With the expansion of Medicaid eligibility, the number of patients with access to transplant care will likely increase. According to Axelrod et al.’s paper “US Health Care Reform and Transplantation,” patients with end-stage renal disease often experience difficulties in accessing private insurance coverage, resulting in suboptimal care for progressive end-stage renal failure, “delayed referral for nephrology and transplant care, [and ultimately] reduced access to transplantation and poor post-transplant outcomes (Axelrod et al., 2010). Axelrod et al. note that Medicare coverage for ESRD patients previously only became “effective at the time of kidney transplantation or after a defined period of dialysis for Medicare-eligible individuals under 65 years old. The expanded legislation through the Affordable Care Act (ACA)] will offer coverage to patients prior to meeting those previous criteria” (Axelrod et al., 2010). Under this reform, insurers are also prohibited from establishing lifetime limits on coverage, rescinding coverage when recipients become ill, or setting preexisting condition exclusions. Thus, the ACA will improve access for ESRD patients to transplant services earlier in the course of their illness, leading to better care and more equitable transplantation access. Further, as lack of private health insurance has often been cited as a barrier to living donation, the ACA can also increase rates of living organ donation (Gibney et al., 2010).

It is important to note that these Medicaid reforms may also present potentially adverse effects on transplant waitlists. An increase in the number of insured patients with earlier access to transplantation could further exacerbate the nation’s alarming organ short-
In fact, according to the Center for Health Strategies, ACOs for a defined patient population (Berwick, 2011). Access may induce worsened post-transplant outcomes by fostering highly coordinated, data-driven, and evidence-based practices. ACOs are thus an effective means of controlling costs and improving patient outcomes. If an ACO succeeds in both delivering high-quality care and reducing the cost of that care below a baseline amount, it will receive a portion of the savings it achieves. The three key facets of ACOs that help to ensure account-
ability are a value-based payment structure, quality improvement metrics, and consistent data collection and analysis. As of March 2016, nine states have launched ACO programs and many have already shown promising results; Colorado’s Regional Care Collaborative Organizations reported a net savings between $29-33 million for Colorado Medicaid in its first three years, while Vermont reported $14.6 million in savings due to its Medicaid ACO program in its first year. Thus, ACOs present an exciting new pathway towards financial sustainability and patient-centered, coordinated healthcare. For Medicare and Medicaid, the organizations may serve as a promising alternative to plans that place the burden of costs onto patients, providers, and private purchasers.

Although many believe ACOs will provide a promising future direction for renal healthcare delivery reform, concerns have been raised that ACOs surrounding patient privacy. With increased information exchange and more eyes on a patient’s health chart, data security and patient privacy may be at increased risk for being compromised. Thus, it will be important for ACOs to ensure strict HIPAA protocols.

II. Affordable Care Organizations

Medicaid Accountable care organizations (ACOs) are voluntary groups of physicians, hospitals, and health care providers that create organized delivery systems for a defined patient population (Berwick, 2011). According to the Center for Health Strategies, ACOs “align provider and payer incentives to focus on value instead of volume, with the goal of keeping patients healthy and costs manageable.” By fostering highly coordinated, data-driven, and evidence-based practices, ACOs are thus an effective means of controlling costs and improving patient outcomes. If an ACO succeeds in both delivering high-quality care and reducing the cost of that care below a baseline amount, it will receive a portion of the savings it achieves. The three key facets of ACOs that help to ensure account-

Inadequate financial losses” (Axelrod, 2010). Medicaid accountable care organizations are becoming increasingly prevalent in state Medicaid delivery systems, and may serve as a potential solution to this problem of inadequate federal reimbursement.

Conclusion

A history of payment reforms in Medicare’s End Stage Renal Disease Program and the Affordable Care Act’s expansion of Medicaid funding and eligibility have reduced dialysis costs and decreased barriers to kidney transplantation for ESRD patients. The two treatment options for ESRD individuals, dialysis and kidney transplant, are expensive and require continual legislative initiatives to balance quality of care with cost containment. Significant progress has been made in the health care delivery of ESRD treatment: the Medicare Prescription Drug, Improvement, and Modernization Act created an efficient, bundled payment system for dialysis treatments, the ESRD Program Amendments eliminated financial barriers to kidney transplantation, and the Health Care and Education Reconciliation Act increased affordability of renal disease medications. Rates of home dialysis, associated with equal levels of quality of care and higher levels of patient comfort than in-facility treatments, are finally beginning to rise, and Medicare reforms have saved a total of $6.1 billion dollars for Americans on prescription drugs through Medicare
coverage. Though the 2010 Affordable Care Act has expanded healthcare coverage, eliminated limits and pre-existing conditions exclusions on insurance plans, increased transplant access, and encouraged living organ donations, the reform also has the potential to further exacerbate the nation’s organ shortage crisis and may place an enormous financial burden on transplant centers and dialysis providers.

Novel healthcare delivery systems, including Accountable Care Organizations, have been developed to regulate the interplay between financial and regulatory changes, health care spending, and quality of care. Although the model is still evolving, Medicaid ACOs offer significant potential for positive change at the provider level to support a healthier population at lower cost, but must follow strict HIPAA protocols so that patient privacy is protected during the collection of ACO quality-assurance data metrics. Moving forward, it is crucial that funding and support are continually given to support ESRD research, and that policy makers communicate with leading researchers in the dialysis and kidney transplant industries, as well as renal patient and professional communities, in considering further health care reform.

The Trump administration and Congress are now beginning to draft negotiations and legislations that are predicted to introduce substantial changes to the United States’ health policy. If Trump follows through on his campaign to dismantle the Affordable Care Act, millions of ESRD patients will receive later access to care, rates of living organ donation will decrease, and insurers may again be allowed to set pre-existing condition exclusions or establish lifetime limits on ESRD coverage. Propositions to change Medicaid in the form of block grants will dramatically decrease the ability of states to pay for low-income citizens’ health insurance coverage. Previously, the federal government would match state spending in the program dollar-for-dollar, with additional money given to states with a larger number of low-income citizens. But with block grants, a single lump sum of money would be delivered to states, without adjustment for low-income populations. Thus, in addition to overall rollbacks in healthcare coverage, the new administrations’ changes in healthcare policy may also create a socioeconomic disparity in treatment and provision of care. With respect to ESRD patients in particular, this decrease in coverage paired with decreased access to early-stage care has the potential to setback federal policy over the past half-century that has worked to improve ESRD patient outcomes.

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Prior to Soviet intervention, Afghanistan was a promising market in the booming South Asian economy. The nation was also popular with western travelers, who savored its rich cultural heritage along the well-traversed Hippie Trail. In 1977, Afghanistan had zero refugees; today, Afghanistan has the second largest population of refugees. Afghanistan in the late twentieth century was evolving into a modernized nation and a leading economic power in South Asia. Despite its relative poverty, Afghanistan’s foreign policy, agricultural production, and health care system were self-sufficient. Less than forty years later, Afghanistan’s foreign policy loses its autonomy to Pakistan, its agricultural industry is nearly nonexistent, healthcare is parlous, and ethnic divides limit the nation’s growth. Afghanistan has become addicted to foreign aid, and although no country in history has improved its economy long-term with foreign aid, Kabul insists for more support and money. Whereas Cold War escapades targeted Moscow and Washington D.C., they struck Kabul.

In a 2002 interview with the New York Times, former US Secretary of Health Tommy Thompson was awe-struck at the obstacles of rebuilding Afghanistan: “It’s hard to appreciate, unless you’ve seen for yourself, the extent to which war and the Taliban have devastated this land and its medical infrastructure … The Afghans have nothing; they need virtually everything.” Earlier that year, while talking with the United States’ Secretary of Health, Afghanistan’s ex-President Hamid Karzai pleaded, “We need to rebuild our health system entirely after 20 years of neglect … [but] most of all, we need you to stay concerned about Afghanistan.”

Fourteen years later, as chaos and strife continuously plagued Afghanistan, health-care systems have further denigrated. Western powers have left the region in conflict and distress, yet Afghanistan’s humanitarian crisis has been forsaken. According to a 2015 report by the World Bank, Afghanistan has the worst average life expectancy in all of Asia: approximately sixty years. During his visit to the nation in 2002, Thompson observed that “the Afghans [still] have nothing; they need virtually everything.”

Exactly how has Afghanistan’s health care system become the worst in Asia?

Ethnic Divides and War

In Afghanistan, war has raged for centuries, from the conquests of the Mongols to contemporary struggles between ethnic factions. Although fighting between the Taliban and the Northern Alliance in the Afghan Civil War destabilized the region in the late twentieth century, ethnic groups have long struggled against each other for land, resources, and ways of life. Afghanistan is home to fourteen distinct ethnic groups, with an ethnically Pashtun majority. Other influential groups include the Tajiks, who represent almost a quarter of the population, as well as the Hazaras and the Uzbeks, each accounting for just under ten percent of Afghanistan’s population. The Pashtun people have long maintained an ethnic control over the Afghan government. Pashtuns are native to Afghanistan’s eastern border with Pakistan, and include Afghan ex-President Hamid Karzai, current president Ashraf Ghani, disproportionate number of government officials, and members of the war-mongering Taliban.

Pashtuns have worked actively since Indo-Pakistani independence in 1947 to gain their own sovereign state, “Pashtunistan,” which may be recognized in the coming future. Bilqees Roshan, a Pashtun senator born near Afghanistan’s border with the Islamic State of Iran, told NPR: “In the past 30 years, ethnicity has been mis-used by people, [particularly ethnic Pashtuns,] trying
to gain more power in the government.” Throughout the 1990s, civil war divided the Afghan government along ethnic lines. While the Pashtun Taliban waged war against the Tajik and Uzbek-backed Northern Alliance, thousands of civilians were massacred and key medical facilities were destroyed on both sides.

The United Nations brought charges against the Taliban at the dawn of the millennia for the mass murder of Hazaras and Tajik civilians. As Hazaras are practicing Shia Muslims, and Pashtuns are Sunni Muslims, the United Nations drew parallels between these violent attacks to the mass murders of Bosnian Muslims during the Yugoslavian Civil War, in which Bosnian Muslims were slaughtered by Slavic Christians due to similar religious differences. Afghanistan has evolved to become one of many playing fields for the Saudi-Iranian conflict, as Sunnis and Shias struggle for control of the Muslim Umma. The Tajik Senator of Northern Afghanistan, Mohammad Alam Ezedayar, shares his birthplace with Mujahedin leader Ahmad Shah Massoud, who was killed leading an anti-Taliban resistance movement. During an NPR interview, Ezedayar discussed his close ties with his fellow Tajiks, claiming that it was their right to have their ethnicity on their identification cards. The Tajiks are a close-knit group of ethnically Persian people. Interestingly, there are more Tajiks in Afghanistan than in Tajikistan. The Tajik people have historically battled the Pashtuns militarily, economically and politically for influence in Afghanistan.

During the nation’s Civil War, ethnic divides spurned world powers to also divide—with the United States, Russia, Iran, and India siding with the Northern Alliance while Pakistan and Saudi Arabia allied with the Mullah Omar-led Taliban. Following the September 11 attacks in the BBC film Putin, Russia, and the West, Russian government official Sergei Ivanov claimed, “The Taliban contacted [Russian] frontier guards on the Tajik-Afghan border. They said they had been sent by Taliban supreme leader Mullah Omar to propose that the Taliban and Russia unite against the United States.” Russia vehemently denied this alliance, however the proposal demonstrates the deep ethnic divides endangering international forces within Afghanistan.

In present day, over sixty percent of Afghans do not have access to electricity, and proposed energy routes look to pass through the Hazara stronghold of Bamiyan or through the Salang pass. The proposed T.U.T.A.P. pipeline (Turkmenistan, Uzbekistan, Tajikistan, Afghanistan and Pakistan) was a multi-million dollar pipeline plan, originally routed through the province of Bamiyan. Melissa Kerr Chiovenda, a Hazara expert at the University of Connecticut commented:

Each time something like this happens, the Hazaras see it as another stone on their backs, they relate it back to a long history of oppression. Bamiyan is seen as the homeland, the seat of the Hazaras. Although the population of the province is relatively small, it’s a symbolic place. This unrest stems from a sense among the Hazaras that the state is not providing for them.

This division in energy consumption and economic interests further divides the nation, spilling onto the global biosphere.

**Afghanistan’s Popular Culture: An Ethnic Schism**

In late 2014, Afghan popular culture also divided along ethnic lines, as Afghan Pashtun General Abdul Wahid Taqat brazenly declared to the Afghan media that “Pashtuns are the rulers and owners of Afghanistan; they are the real inhabitants of Afghanistan ... Afghanistan means ‘where Pashtuns live.’” General Taqat’s comments faced strong opposition by leading figures in Tajik, Uzbek, and Hazara-dominated areas of Afghanistan—further entrenching ethnic divisions. General Taqat’s nativist attitudes towards minorities in the nation has been used to justify the persecution of Hazaras, Tajiks, and Uzbeks.
Ethnic Divides and Health Care

Ethnic divides rattle Afghan health care. During its oppressive regime, the Afghan Taliban destroyed innumerable health clinics, raging chaos on the Afghan health care system. As part of their strict legal code, the Taliban banned portrayals of the human body, including medical textbooks. In Pakistan’s Khyber Pakhtunkhwa Province, which held a major health care center for Afghans, 29% of health facilities were destroyed by the Taliban, undermining national health care. The Taliban continues to show disregard for health care facilities, as seen in the skinning of a Fazl Ahmad, a young Afghan man accused of being the distant relative of another man who allegedly killed a Taliban commander last June. Admittedly, Afghanistan has long been an area of turbulence, spanning from the conquests of Tamerlane and Babur to the Soviet Invasion of the mid-twentieth century and into the present day. As invaders thwart each other in Afghanistan, health care facilities will continue to crumble.

Afghanistan’s humanitarian crisis has been compounded by ethnic tensions. The United Nations Office for Coordination of Humanitarian Affairs shows that 700,000 Afghans are without emergency shelter; 1.7 million lack food security; 2.9 million nutrition; 1.7 million protection; 1.5 million water, sanitation, and hygiene; and 3.1 million health. The UNOCHA further shows that 1,900 civilians were killed and 137 thousand civilians displaced in 2016 during the standoff between the Taliban and its adversaries. The Afghan people suffer from the most horrific health care system in Asia. Seemingly insurmountable poverty, decaying infrastructure, and a landmine crisis plague the nation. Life expectancy is approximately 60 years—eighteen years shorter than the United States—and a quarter of children die before reaching their fifth birthdays. Diseases such as chronic malnutrition, cholera, Congo-Crimea Fever, diarrhea, and measles have been eradicated in the West, but kill scores of Afghans daily. Landmines from the time of the Mujahedin, laid by Taliban militants, kill more people than in any other country. Physicians are at a premium in Afghanistan. There is 1 doctor for roughly every 50,000 people in Afghanistan, while the United States has approximately 1 doctor for every 350 people. When WHO representatives visited Afghanistan in 2002, only three out of 133 hospitals surveyed were designated as acceptable.

Due to its frequent ethnic-centric warfare, Afghanistan is one of the world’s most mined nations. Only two of Afghanistan’s twenty-nine provinces are mine-free. According to the International Committee of the Red Cross, children compose the majority of landmine casualties in Afghanistan. In a PHR study in 2001, representatives surveying Afghan women noted poor mental health and suicidal thoughts: “The majority of respondents (63-87%) described their physical health as ‘fair’ or ‘poor.’” While numerous health care advocacy groups have entered Afghanistan, locals scarred by invaders of centuries past are hesitant to accept foreign intervention. However, Afghanistan continues to improve its health infrastructure. Although public health care coverage is only 70%, it has increased by over 20% since the turn of the century, according to a recent WHO report. Foreign resistance to the Taliban has also decimated Afghanistan’s infrastructure. In later 2015, a coalition led by the United States bombed a hospital in Kunduz. In the attack 44 patients, including women and children, were killed. Although the United States military has accredited mechanical and communication failures as causes to this humanitarian catastrophe, journalist Matthieu Aikins of New York Times Magazine postulates that Afghan forces led the Americans into the attack on the hospital because it was believed to be harboring Taliban fighters.

Afghanistan has placed a high priority on improving health infrastructure. Afghanistan works to restore its health care facilities, expand coverage into

Men outside the Boost Hospital in Lashkar Gah guard the complex from potential attacks. Fighting is prevalent in the surrounding districts of Nad Ali, Marja, Geremshir, and Nawa.
rural areas, increase the amount of medical treatments available to Afghans, facilitate an increase in health care workers, and improve Afghanistan’s resilience for natural disasters. In his book, Fixing Failed States: A Framework for Rebuilding a Fractured World, Afghan President Ghani looks to rebuild Afghanistan’s infrastructure to remedy its collapsing health care system. However, Afghanistan spends over half of its annual 1.8 Billion USD government budget on national security, giving Afghan health care systems little financial hope for recovery.

While Afghanistan’s health care system is in disarray, the Afghan people continue to work towards a brighter future. Current efforts to repatriate Afghan refugees as well as to reconstruct medical facilities and schools will help the nation resolve its ethnic schism and rebuild from the devastation of recent warfare. Although Afghanistan currently possesses Asia’s worst health care system, Afghanistan can potentially become a leader in South Asian health care once again through cooperation between ethnic groups and foreign aid. Despite ethnic divisions and conflict that divide the nation culturally, politically, and socially, Afghanistan’s health care system could recover to its twentieth-century zenith, when Afghan foreign policy, agricultural production, and health care system will all once again be self-sufficient. The Afghan people may need “to rebuild [their] health system entirely after 20 years of neglect … [but] most of all, [they] need you to stay concerned about Afghanistan” to improve their outlook for a better future.

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Umma: the whole community of Muslims bound together by ties of religion.

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Born from Hispanic immigrant parents, I am familiar with the importance of effective communication when it comes to accessing resources. Therefore, it is concerning that over 60.6 million people nationwide are limited by language barriers. Within our healthcare system, language barriers are restricting patient-doctor interactions. This unfortunate reality prevents millions of patients from accessing adequate care every day.

Anne Fadiman, recipient of the National Book Critics Circle Award, documented one of such language barrier cases in her book, The Spirit Catches You and You Fall Down. She describes the challenges faced between two Hmong parents and their daughter. Though the doctors claimed Lia was suffering from epilepsy, the parents believed their daughter was bound by a dab (evil spirit). In the end, because of miscommunications and cultural differences, the parents did not administer the proper drug dosages. Unfortunately, Lia ended in a vegetative state.

It’s more common than we think. From my volunteer service at Huntington Hospital, I saw that medical knowledge alone cannot complete a physician. Often, I witnessed language barriers between medical staff and patients. Once, I saw a mother try to communicate a simple human need: More food. The patient shaped her hands into a bowl. When that failed, she tried cupping them. Finally, in frustration, she ceased by pretending to jab the table with a fork. None of us understood. It wasn’t the patient’s fault. It was our fault: Four employees and none of us knew her language.

According to Title VI of the Civil Rights Act of 1964, the denial or delay of medical care because of language barriers constitutes discrimination. Therefore, hospitals are required to provide language services. However, the Office of Civil Rights allows hospitals to opt out of this protocol if budgets are too tight. Hence, hospitals rely on ad hoc interpreters—family members, friends, and untrained staff. It is important to note that these individuals are not adequate substitutions. They have not received prior medical training and may not be able to interpret complex medical terms. This may result in a miscommunication between patients and doctors which could lead to detrimental consequences.

In order to run an effective practice, effective communication is just as essential as the actual clinical procedures. Therefore, medical schools should place a greater importance on learning additional languages. Our nation’s demographics are becoming more and more diverse. Our patients increasingly represent cultural and linguistic backgrounds from every corner of the globe. It is imperative for members of the medical staff community to learn another language. A patient would surely feel more comfortable communicating and attentively listening to a clinician who speaks in the same language. Furthermore, a staff member fluent in more than one language will not only strengthen her linguistic communication skills, but also her cultural competency with a diverse range of patients. Of course, actualizing this vision would require the support of the American Association of Medical Colleges (AAMC) and the greater medical community.

In addition, hospitals and clinical offices should re-adjust their budgets to incorporate more interpreters: Full-time, part-time, or on-call. It only makes sense. Take the judicial system. According to Title XXVIII of the U.S. Constitution, an interpreter must be provided if needed in a court case. It ensures that those involved have equal access to justice. Therefore, why is it that an interpreter cannot be provided for every medical case? Have we become accustomed to pursuing malpractice lawsuits instead?

Contrary to common belief, hiring more interpreters does not carry much of a financial burden. According to an article published by Yale School of Public Health, it only costs $17.77 per request for an interpreter. It would be costlier to continue feeding language barriers than invest in supporting the health of a growing population.
Allotting funds to pay interpreters is worth it. They will alleviate the responsibility from patients’ family and friends, ensure that medical terms are correctly translated, and maintain proper patient confidentiality. More importantly, though, it will guarantee that patients fully understand the procedures they are undergoing and treatments that they must self-administer at home.

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INVESTIGATION

The investigation section presents and analyzes pressing public health issues through the lens of epidemiological, medical, and scientific perspectives.
Abstract

In 2012, Hantavirus—an RNA virus that is commonly carried by mice—impacted overnight tourists who camped at Yosemite National Park. I will be exploring the particular cultural and historical setting of Hantavirus, specifically Sin Nombre virus. Literature regarding the Yosemite Hantavirus outbreak will answer two essential questions: 1) What are the short-term societal impacts of the Yosemite outbreak? 2) What are the long-term societal impacts of the Yosemite outbreak? These two questions will be analyzed based on the contexts of local versus global impacts and positive versus negative impacts. By understanding the impacts of Hantavirus on the surrounding community, I hope to highlight the strengths and weaknesses of current and past response protocols and encourage more effective preparation for future Hantavirus outbreaks.

Introduction and Background

Hantavirus causes two specific health complications: Hantavirus Pulmonary Syndrome (HPS) and Hemorrhagic Fever with Renal Syndrome (HFRS) ("Hantavirus", 2016). HPS, commonly caused by the Sin Nombre virus, directly impacts the respiratory system causing early flu-like symptoms including fever, muscle aches, headaches, vomiting, nausea, diarrhea, dizziness, and chills. Late symptoms—approximately four to five days post early symptoms—of HPS include fluid build-up in the lungs and dyspnea (shortness of breath). HPS is commonly found in the New World (including North and South America) Hantavirus. Deer mice and rats are reservoirs for Hantavirus in the New World, and humans can contract the virus by coming into contact with or breathing in virus from infected rodent urine, feces, and saliva. Human to human transmission of Hantavirus has not been reported (Safronetz et al., 2016, p. 7114-7119). HFRS is a form of Hantavirus commonly found in the Old World—Asia and Europe—and includes Seoul virus carried by Rattus rattus, Puumala virus carried by Myodes glareolus, Dobrava virus carried by Apodemus flavicollis, and Saaremaa virus carried by Apodemus agrarius. Similar to the Sin Nombre virus, the Old World Hantavirus can be transmitted to humans by exposure or contact with rodent urine, feces, or bodily fluids. Symptoms of HFRS also include nausea, fever, chills, abdominal pain, and blurred vision. However, the late symptoms of HFRS are more severe than those of HPS and possess a 5-15% fatality rate for patients in the United States. Late symptoms include vascular leakage, severe hypotension, and acute kidney failure ("Hemorrhagic Fever with Renal Syndrome HFRS", 2008, p. 508-509).

HPS and HFRS are often misdiagnosed during the initial stages due to similarities with the common cold and influenza. However, patients who state previous or potential exposure to rodent infested environments complete serologic testing for Hantavirus antigen presence via immunohistochemical staining. Specific diagnostic measures for HFRS include thrombocytopenia (low number of platelets), urine tests for high levels of albumin, and urine tests for blood presence. ELISA, immunofluorescence staining, and thrombocytopenia are used as diagnostic measures for HPS (MacNeil, 2011, p. 238-140). No antiviral drugs or vaccinations are available for Hantavirus; therefore, treatments are catered towards regulating symptoms (Lee, 1996, p. 253-257). Early detection of Hantavirus will allow for more effective treatment of the symptoms including careful fluid and electrolyte monitoring for HFRS and oxygen therapy for severe cases of respiratory distress for HPS (Cosgriff, 1991, p. 97-98). The pathophysiology of Hantavirus impacts the epidemiological response towards HPS and HFRS, particularly the Yosemite HPS outbreak.

Societal History of Hantavirus Internationally

HFRS first shed light on the international impacts of Hantavirus, when approximately 3,000 cases of the disease were reported in South Korea in 1951, a time when UN forces were fighting on the 38th parallel
during the Korean War. HFRS had most likely been present in Eurasia, specifically Korea, Manchuria, and Russia, for centuries with the first records found in 1913; a milder account of Puumala fever was discovered in Finland in the early 1930s (Cameron, 2011, p. 1289-1290). Hantaan virus (HTNV) surveillance demonstrated the presence of viruses similar to that of HTNV in Far East Asia, China, and South Korea in the following species of rodents: Apodemus agrarius and A. peninsulae. In Europe, the Dobrava virus was found in the following species of rodents: Apodemus flavicollis, A. agrarius, and A. ponticus.

Recorded cases of Asian urban HFRS in the 1980s are linked to the Seoul virus in Asian, and recorded cases of European urban nephropathia epidemic (a milder version of HFRS) in the 1930s are linked to the Puumala virus (Jonsson, 2010, p. 420-421). With the greater availability of the Hantavirus antigen, urban rodents (Rattv. norvegicus and Rattus rattus) have been found to harbor the virus after transmission from humans. This urbanized version of HFRS has now been serologically identified in North and South America, New Guinea, India, the pacific islands (including the Philippines, Hawaii, Taiwan, and Fiji), and Africa. Isolated forms of the Hantavirus have been reported to be in use for medical research in Japan, Belgium, France, United Kingdom, and Korea. Currently, HFRS remains an international public health threat as approximately 150,000-200,000 patients are hospitalized due to Hantavirus (Lee, 1996, p. 260-265). With the globalization of medicine through advanced transportation and communication, both the Hantavirus disease and people’s awareness of the disease have spread across the world.

**Societal History of Sin Nombre Virus in the United States**

Previous cases of HFRS in the United States were reported around 1862 and 1863—during the Civil War era; however, the lack of serological testing prevented confirmation of Hantavirus. The first recorded outbreak of Hantavirus was in 1993 in the Four Corners (Arizona, Colorado, New Mexico, and Utah). The Hantavirus in the Four Corners was characterized by the HPS causing virus Sin Nombre. Serological testing of Sin Nombre represented a cross reactivity between the Old World Hantavirus (HFRS) and human sera (Jonsson, 2010, p. 437-439). The first reported patient of the 1993 outbreak was a previously physically fit and healthy Navajo man from New Mexico, who experienced shortness of breath and died shortly afterwards, and his fiancé had died several days before, demonstrating similar symptoms of respiratory distress. Dr. Bruce Tempest of the Indian Health Service then identified five additional previously healthy patients who died of acute respiratory distress. After serological testing failed to identify the cause of death, the following departments were immediately notified: Center for Disease (CDC), the Indian Health Service, the University of New Mexico, the Navajo nation, as well as the state health departments of New Mexico, Colorado, and Utah. In order to determine the natural reservoirs for the unknown virus, rodents found near or inside the living areas of the patients were trapped and used for tissue testing. After approximately 1,700 rodent trappings, the virus was finally isolated in November 1993 and identified as the Sin Nombre virus (Khan, 1997, p. 1297-3000). The surge of the HPS outbreak in 1993 is attributed to a drastic increase in the rodent population after a long drought period. The high number of mice increased the chances of human-rodent exposure.

In an analysis of the first one hundred patients in the United States infected with HPS since 1993, Hantavirus outbreaks were common during the spring and early-summer timeline. There was not a significant gender difference; 54% of patients were males. The ethnic distribution of the first one hundred patients was 63% Caucasian, 35% Native American, and 2% African American, and the average age for the cases was 34.9 years (Ksiazek, 1995, p. 121-124). Through tight regulation and early diagnosis measures, the Hantavirus outbreak is being monitored and regulated from reaching pandemic levels; however, Hantavirus HPS continued to impact people in the United States. From 1993 through 2011, HPS has impacted 587 people in the United States. In the summer of 2012, Hantavirus reemerged, attacking tourists visiting Yosemite National Park.

**Short-Term Societal Impacts of the Yosemite Hantavirus**

Initially, ten tourists from three different states who stayed overnight at Yosemite National Park were ex-
experiencing respiratory complications, characteristic of HPS symptoms. For the first eight patients who were identified, five required ventilator assistance in the intensive care unit and the other three patients died. After surveying the patients, nine out of ten tourists resided in the Curry Village Yosemite signature tent cabins overnight, which were marked by rodent nests and tunnels in the foam insulation of the walls. 50% of tourists who stayed in signature tents were from California, 30% from other states, and 20% from other countries. For epidemiological analysis, 73 deer mice were trapped and completed serological testing, and 14% of the trapped mice tested positive for Sin Nombre virus. Patients who were infected with HPS engaged in similar activities as tourists not impacted by the disease. As an immediate short-term response to the Yosemite outbreak, the park shut down and dismantled all 91 signature tents to prevent further transmission. 1,300 buildings were inspected, rodent exclusion practices were performed when necessary, and rodent population surveillance was put into place via various trappings throughout the park. (Hartline, 2013, p. 978-982). Addressing this outbreak incentivized the collaboration of the CDC, California Department of Public Health (CDPH), and the National Park Service (NPS) Office of Public Health.

From August 27th to September 17th, 2012, the park presented every tourists with informational handouts regarding Hantavirus, posted educational messages in common areas, and trained park employees about preventative measures. The park also contacted approximately 10,000 tourists who had stayed overnight in the signature cabins and encouraged them to immediately seek medical attention if they presented any symptoms of HPS. The Yosemite outbreak was different from that of the 1993 outbreak due to the quick spread of the disease but also quicker identification and response to the disease. The patients from the Yosemite outbreak were also exposed to a smaller geographic region than the patients from the four corners (Nunez, 2014, p. 386-393). However, the previous response tactics that were implemented during the 1993 outbreak aided the efforts to tackle the Yosemite outbreak.

Because 20% of tourists were from countries outside of the United States, the park officials meticulously analyzed paperwork for all international visitors and contacted public health officials for 39 countries. One specific example includes the UK’s response towards the Yosemite outbreak. The UK Health Protection Agency used information from the US National Park Service to contact approximately one hundred travelers deemed to have a high risk of being exposed to Sin Nombre. This response allowed for public media coverage and publications in academia (e.g. Vanya Gant’s paper regarding the Yosemite outbreak in the New England Journal of Medicine), furthering awareness of the disease and its symptoms (Roehr, 2012). This collaborative response on an international scale exemplified the advantages of quick acknowledgment and notification of zoonotic outbreaks.

Long-Term Societal Impacts of the Yosemite Hantavirus

The Hantavirus outbreak only temporarily impacted the tourism industry for Yosemite National Park. The quick response and additional precautionary measures encouraged more tourism after the successful suppression of HPS. Currently, tourism in Yosemite National Park generates over $378 million each year and involves 5,162 jobs for the local community (“Economics”, 2015). The Yosemite outbreak lead to the restructuring of preventative measures for park employees. The program emphasizes extensive use of cleaning practices, use of personal protective equipment (PPE), and education of Hantavirus safety training and knowledge of HPS (Wilken, 2015, p. 663-664). The high fatality and quick spread of the Yosemite HPS outbreak prompted the international medical community to conduct further research on the development of a Hantavirus vaccination.

Hantavax, a Korean Hantaan virus vaccine, demonstrated high antibody titers and neutralizing antibodies over the course of a twelve-month vaccination period. No serious adverse effects were reported; therefore, Hantavax is a potential vaccination that may be introduced by the World Health Organization after further testing. Pharmaceutical companies were reluctant to fund Hantavirus vaccinations due to the low instances of Hantaan infections in the majority of the world, especially since Hantavirus has been reported in countries well-equipped with medical resources to aid patients without the need for antiviral drugs or vaccinations;
however, the Yosemite outbreak once again reminded the medical community of the advantages of a Hantavirus vaccination as a crucial preventative measure (Maes, 2009, p. 68-73). Because Hantavirus is indiscriminate and can impact people regardless of socioeconomic standards, gender, or ethnicity, the Yosemite outbreak was an important stimulus for raising awareness regarding its global impacts.

Conclusion

Hantavirus has existed in society for centuries as HPS and HFRS, impacting patients from Asia to the United States. As the medical community conducts further research regarding HPS and HFRS, the virus continues to adapt to the changing environment. The 2012 Yosemite outbreak served as a reminder that effective public health responses, communication between various healthcare departments, and development of novel preventative measures regarding Hantavirus are necessary in combatting this ever-changing disease.

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I walked into a nutrition and health store in Palo Alto, California, as a customer was returning a bottle of exercise supplements. “It was giving me weird heart rates,” he told the sales associate. After refunding the customer, the associate asked him to check out a brand new supplement and its “advanced formula for working out.” The customer inspected the product and retorted, “These are not regulated by the FDA [U.S. Food and Drug Administration] or government, right?” The associate promptly replied, “Not by the FDA, thank God. If they did, we would never see them in our stores.”

The sports supplementation industry capitalizes on growing trends of self-medicating consumers seeking an “ideal” body type. Advertisements for sports nutrition products (SNPs) want us to believe the idealistic human figure is athletically built and completely toned. In the U.S., a quarter of adults aged 18 and over are estimated to take some form of sport supplement.1 Furthermore, the U.S. is the largest market for sports nutrition with sales reaching $6.7 billion in 2015.2 McKinsey & Company analysts attribute market growth to an increased awareness for preventative care, the development of self-directed consumers, and targeted marketing campaigns.3 These trends work together to pump wealth into the veins of sports nutrition companies worldwide.

A combination of factors culminates in the current state of affairs. First, lack of pre-market FDA regulation allows for a constant evolution of new products without governmental quality control. Secondly, millions of people are buying SNPs under the assumption that they’re safe. Finally, sly marketing tactics manipulate consumers with extreme claims and alluring packaging. To break this vicious cycle, people must realize the hidden dangers of SNPs through accessible resources that expose their inadequacy and the aberrant malpractice of their companies. These shortcomings are emphasized by the following section titles that incorporate the cautionary statements found on SNP labels. By addressing their regulation, safety, and marketing, I am going to delve into why ceasing the purchase of SNPs is a wise choice to protect our health.

“This statement has not been evaluated by the Food and Drug Administration”: Untamed and Unregulated Products

Why do SNPs remain unregulated? The FDA was established to protect the public against health hazards, pithily conveyed in their slogan, “Protecting and Promoting Your Health.”4 However, there is a discrepancy between our presumptions and their principal obligations. The FDA’s regulatory power is limited due to the Dietary Health and Supplement Education Act (DHSEA) of 1994, which excludes “dietary supplements” (including SNPs) from food and prescription drug regulations.5 Sports nutrition companies are thus responsible for their own evaluations of product safety and labeling before they reach the market.6

To clarify, selling adulterated or mislabeled products remains illegal, but sports nutrition manufacturers and distributors “are not required to get FDA approval before producing or selling” their products.6 No groups or agencies need to test these products unless manufacturers pursue regulatory validation. A primary method of discovering contaminated or misbranded products are Adverse Event Reports that notify the FDA of believed malpractice within the sports nutrition market.6 However, the FDA does not seek out violations of regulatory validation; existing ones are presented, and the FDA is responsible for operating retroactively.

Despite aforementioned deficiencies, there is still hope for the FDA’s proactive efforts concerning SNP regulation. In 2011, the FDA released a groundbreaking draft on industry guidance for “new dietary ingredients,” defined as those not used in supplements before 1994, when the DHSEA was enacted.7 In a review of the industry guidance, Harvard Assistant Professor of Medicine Dr. Pieter Cohen affirms that “the proposed guidance clarifies the level of evidence the FDA would
use to assess safety,” but he does not believe “the FDA has gone far enough” in regards to requiring companies to produce fresh and conclusive experimental data for the safety of new ingredients. This new industry guidance would be a step towards additional pre-market regulation, but its implementation is hindered because the FDA is still working on revisions.

Currently, a company’s credibility can be verified mainly through the optional regulation it seeks, such as by reliable third-party testing groups which are free from conflicts of interest and are further accredited by external organizations. A prime example is the National Science Foundation (NSF), recognized by the U.S. Anti-Doping Agency (USADA) and major league sports associations. The foundation uses the NSF/ANSI 173 standard, which is “the only standard currently available for evaluating dietary supplements” such as SNPs. The NSF investigates product adulteration and crosschecks labels against contents to provide high-quality safety information for consumers. Unfortunately, there are only 623 SNPs certified by the NSF compared to thousands that are not.

Being aware of a trustworthy testing source is helpful, and so is the ability to research the track record of individual companies. The FDA’s previously mentioned reporting service keeps track of adverse events such as possible company malpractice and potentially harmful products and makes this information publicly available to consumers. A major drawback is the system’s reactionary nature; substantial reports on newly marketed supplements are unlikely. Nonetheless, scanning a company’s FDA track record could provide helpful information to facilitate informed decisions before purchasing a product.

“Consult with your physician before using this product”: What You See is Not What You Get with SNPs

Unfortunately, many SNPs end up adulterated or mislabeled, and third-party studies quantify the scope of harmful substances on the market. For example, in 2008, Dr. Hans Geyer and colleagues analyzed the composition of 634 SNPs from 13 countries for the presence of potentially dangerous substances not represented on the label. Almost one in five products were contaminated with anabolic steroids. In 2006, a similar study by Baume et al. concluded that contaminated products “could lead to several and unintentional consequences on morphological appearance and behavior. Depending on the time period of the treatment, these psychological and physiological effects could be dangerous and irreversible for the consumer.” One in five companies makes billions of dollars by selling hazardous products to millions of people, which is doubtlessly cause for concern.

Moreover, it is also vital that consumers understand even “good” SNPs do not have consistent scientific bases for effectiveness. The FDA requires companies to notify them if their product contains ingredients not marketed before 1994, when the DHSEA was enacted. For post-1994 “new ingredients,” companies are allowed to use past findings from scientific literature to demonstrate the benefits of the components in their product. Unfortunately, the referenced literature could have studied a different dosage or delivery method making it difficult to assess product effectiveness in humans. Furthermore, the FDA acknowledges that “there is no authoritative list of dietary ingredients that were marketed in dietary supplements before October 15, 1994,” which means companies decide if they will submit a “new ingredient” notification or not. Again, we see that regulatory responsibility belongs to the companies themselves.

The shocking outbreak of acute non-viral hepatitis (non-contagious liver inflammation) in Hawaii in 2013 exemplifies the hazards of seemingly unadulterated SNPs. Described by Johnston et al. as “one of the largest statewide outbreaks of dietary supplement-associated hepatotoxicity,” this spate of life-threatening liver problems was linked with ingestion of OxyELITE Pro®, a weight loss and energy supplement created by USPlabs®. Deplorably, two patients required liver transplants and one patient died as a result. State investigators screened the product in conjunction with the FDA and confirmed, “analysis found consumed products were consistent with labeled ingredients [of OxyELITE Pro™]” with no evidence of overdosing reported.

Yet one ingredient, aegeline, worried the FDA. They deemed it a “new dietary ingredient” and issued USPlabs® a warning letter to cease product distribution because the company failed to provide safety infor-
As previously stated, there is no definitive list for new dietary ingredients, but on November 17, 2015, the U.S. Justice Department indicted six USPlabs® executives for involvement in the adulteration of OxyELITE Pro™ with “synthetic” stimulant drugs: 1,3-dimethylamylamine (DMAA) and aegeline.16 Relatedly, the USADA warns that no regulatory body can test for all substances, and it is difficult to analyze adulterated products with the continuous evolution of synthetic “designer drugs.” During the study conducted by Johnston et al., researchers could not pinpoint which ingredient caused the non-viral hepatitis, but recently aegeline was linked to the disease outbreak.

This case study brings us back to the NSF. With the NSF/ANSI 173 standard, the foundation assures “a dietary supplement contains the ingredients claimed on the label, either qualitatively or quantitatively, and that it does not contain specific undeclared contaminants.”17 However, synthetic and newly evolving ingredients can elude current scientific analyses, such as in the case of aegeline. Additionally, the NSF and other organizations do not check the validity of products’ claims, an astonishing fact that Dr. Cohen confirmed when I reached out to him for comment. In fact, “no one tests for efficacy of supplement products,” he said, “given the current regulatory environment, consumers are not able to obtain accurate information about [the claims of] supplements on store shelves.”18 This account is not meant as an attack on reputable organizations, rather a sobering realization that billions of dollars are spent on products that modern science has difficulty proving safe and effective for humans.

“Please Read the Entire Label Before Use”: Unreasonable Promises and Exploitative Marketing

Millions of people are buying SNPs in pursuit of fitter bodies. With regulatory ignorance and a lack of a convincing body of evidence, negligent supplement companies manipulate the public’s understanding in attempts to exploit desires to improve health. SNP marketing targets consumers’ aspirations, openly illustrated by the advertisements and images they use. The most obvious examples are photographs of hyper-fit men and women emblazoned on product labels or advertising campaigns. In Visual Persuasion: The Role of Images in Advertising, University of Pennsylvania Professor Paul Messaris notes, “photographs supply crucial documentation, without which an ad can lose much of its power to convince the viewer.”19 Though a simple strategy, images of perfectly toned individuals juxtaposed with a company’s products visually influence a consumer to link them together.

Beyond graphics, companies market and label their products primarily through structural and functional claims focused on beneficial effects.6 For most dietary supplement claims, U.S. law “does not require the manufacturer or seller to prove to FDA’s satisfaction that the claim is accurate or truthful before it appears on the product.”20 As resources permit, the FDA will monitor supplement labels after a product has entered the market.20 This level of labeling autonomy and the extrapolation of scientific data mentioned in the first section allow companies to make bold claims about how their products work. For example, a sports supplement could state it “supports extreme muscle building power,” or “promotes maximum energy performance.” Eloquent diction is entertaining to read — sometimes highly enticing — but the devil is often in the details, and the details are in the asterisks associated with SNP claims. The fine print of SNPs provides disclaimers that the FDA has not evaluated claims and the products are not meant to diagnose, treat, cure, or prevent any disease.6 The asterisk is a symbolic reminder hidden in plain sight that SNPs have not been rigorously tested for their safety and efficacy within the human body. The alluring statements of SNPs capture attention and intrigue as intended, but desires for a better body fall prey to their often misleading promises.

Calling for a Culture Shift

Resources providing insight into the safety and efficacy of SNPs indicates a lack thereof. Absence of appropriate regulation, unfounded scientific claims, and exploitative marketing perpetuate a vicious cycle that makes SNPs dangerous to consumers. Even though research clearly exposes the dangers of SNPs, people will inevitably still purchase them. SNPs are a growing billion-dollar industry, and they are marketed as a shortcut to fitness. At the very least, consumers should minimize the potential for harm by evaluating sports nutrition companies and their products through resources such as FDA records.
and NSF regulation. Third-party testing can identify “safer” SNPs, but synthetic additives can still evade toxicity analyses. No resource can protect you from all malpractice, no organization tests for product efficacy, and there is no guarantee that SNPs work. As individuals, we have the freedom to choose our nutrient sources. Rejecting the use of these products is a safe and smart option, because we can threaten our health by using SNPs for the sake of it.

References


Approximately 1.2 million people in the world live in extreme poverty. It is an accurate observation that living in poverty causes inadequate access to healthcare ultimately leading to poor health outcomes in patients. However, how is the extent of these poor outcomes examined as different poverty levels across the world are analyzed? Tara Templin, Stanford University Department of Statistics, tackles this issue and provides insight into how we can assess the connection of poor health outcomes in different poverty thresholds.

On January 18th, Tara Templin, Annie Haakenstad (Harvard T.H. Chan School of Public Health), Abigail Chapin, and Joseph Dieleman (University of Washington), presented their abstract at the 3rd annual global health research convening at Stanford University. Templin’s research focuses on addressing and demonstrating that poverty and mean national income account for the variation in health outcomes across patients. Templin accomplished this through constructing 51 different poverty series measured at different poverty thresholds, using 188 different countries. Her project was further motivated by the large inaccuracies in the POVCAL data sets given by the World Bank. It was found that 86% of the data in the POVCAL system was either inaccurate or missing. These series were then tested and analyzed in order to see which poverty threshold benefited the most relative to others. From here, we can determine how specific poverty levels in a nation relate to specific healthcare factors such as: access, treatment, and outcome.

A three step process was used for the prediction of these data sets. Upon constructing 51 different poverty series, 2,578 potential covariates are considered. These covariates are provided from the World Bank, Institute for Health Metrics and Evaluation, Freedom House, and the Quality of Government databases. From here, Bayesian model selection and the categorization of covariates was implemented. This data is then separated into three different models: multiple imputation, hierarchical mixed effects models, and Gaussian Process Regression. A hierarchical model imposes a structure that allows for the comparison of different countries in order to show ways in which they relate. Cross validation is used in order to check the validity of these data sets and the Gaussian Model allows for the determination of the best model. These models are also tested against certain societal factors such as GDP, poverty and HIV. Testing GDP against certain factors such as GDP with the regression effect is to test the effect of poverty above and beyond terms of GDP. This data is significantly important in determining if national poverty rates are related with changes in adult and child mortality. This research is extremely useful in predicting trends in poverty levels and their connections with healthcare.

The studies published by Tara Templin are extremely beneficial in understanding the relationships between income/poverty levels and how they play out in the implementation of healthcare across the globe. Poverty is much more associated with healthcare outcomes beyond the scope of just gross domestic product. For example, getting out of extreme poverty ($1.25/day) does not significantly improve one’s health. A patient’s health can only significantly improve when a patient avoids living in “extreme poverty” defined at $5/day.

Fully addressing the issue of access to adequate healthcare is still far from complete, however progress has certainly been made. By redefining poverty levels and assessing health outcomes at this point, Templin has paved the way for a new perspective in achieving improved national health.

References

Introduction

A mosquito is a slender, long-legged fly; however, this insect is the most deadly animal in the world. The term “mosquito” is misleading; it is Spanish for “little fly.” However, there is nothing “little” about the one million deaths worldwide that mosquitoes are responsible for annually (American Mosquito Control Association). Mosquitoes are disease vectors with the ability to carry and transmit viral diseases to other living organisms. They are responsible for the transmission of several dangerous diseases, such as malaria, West Nile virus, dengue fever, and Zika virus. Malaria is the most deadly of mosquito-borne diseases, killing one child every 40 seconds and affecting over half a billion people annually (American Mosquito Control Association). In hopes of developing preventative measures to control future mosquito-borne disease outbreaks, medical researchers have focused on identifying the primary factors that can accelerate the spread of such dangerous diseases. One possible, though controversial, factor is global climate change.

Medical researchers differ in their willingness to attribute climate change to the increased distribution of mosquito-borne diseases. While vector biologists tend to feel as though climate change’s drastic increase in global temperatures is insignificant and overshadowed by a myriad of other human factors, more environmentally-minded medical researchers argue that climate change will increase the distribution of mosquitoes globally and thus increase the incidence of infectious diseases. An overwhelming majority of experts in the field of epidemiology believe that various socio-economic, demographic, and environmental factors are just as responsible as climate change in influencing the prevalence of mosquito-borne diseases. While each side of this debate supports their differing arguments through the use of statistics, predictive models, and past research, the purpose of the debate is obscured in the process.

Climate change’s influence on mosquito-borne diseases is of much discussion; however, the relationship between climate change and disease transmission will not alter the measures taken to control disease outbreaks because climate change is caused by the same human behaviors that medical researchers agree contribute to the spread of mosquito-borne diseases. As a result, rather than conducting long-term studies to better understand climate change’s direct impact on mosquito-borne diseases, medical researchers should prioritize tackling human factors, such as deforestation, urbanization, and water control projects, that lead to both climate change and the increased prevalence of infectious diseases.

The Misunderstood Debate: Climate Change’s Controversial Role

The lack of long term studies analyzing the relationship between climate change and disease dynamics causes researchers to rely on their unique disciplinary backgrounds and the differing temporal frameworks of their evidence in interpreting the significance of their similar observations. The various conclusions that medical researchers draw from seemingly objective facts shape the debate, but the divergence of these conclusions hinder immediate action.

Vector biologists, such as Paul Reiter, downplay climate change’s influence on vector-borne diseases, believing that the behavioral factors of both humans and vectors have more direct ties to the incidence of infectious diseases. However, public health experts, such as Paul Epstein, an Associate Director of the Center for Health and the Global Environmental at Harvard Medical School, believe that altering climatic patterns pose favorable conditions for mosquitoes to carry and transmit infectious diseases. While Epstein and Reiter both acknowledge the expanded distribution of mosquito populations, Epstein is more likely than Reiter to attribute such an observation to climate change because of his background in public health. Epstein writes in his Scientific American journal entry, that “the case for a climatic contribution becomes stron-
ger...when other projected consequences of global warming appear in concert with disease outbreaks” (Epstein, 2000). This, he believes, is the case in highlands around the world, for “mosquitoes, once limited by temperature thresholds to low altitudes...are being reported at high elevations in South and Central America, Asia, and east and central Africa” (Epstein, 2000). These climate change indicators, however, are the same indicators that Paul Reiter exposes as deceptive in his most recent article, “Global warming and malaria: knowing the horse before hitching the cart.”

Reiter, a medical entomologist and member of the World Health Organization Expert Advisory Committee on Vector Biology and Control, believes the reemergence of mosquito populations in many highland areas has more to do with the interaction between human behavior and mosquito biology than climate. According to Reiter, “Nairobi was well known for its malaria” and “had big problem with malaria...after World War I, when a lot of white people started settling in the Kenya highlands. [This problem] continued until the advent of DDT in the 1950s” (EIR, 2007).

Reiter uses the history of human-host interactions in African countries as evidence to refute Epstein’s argument that climate change is bringing about the introduction of mosquito-borne diseases in unexpected regions. As a public health researcher, Epstein uses current outlooks on climate change to predict how this global phenomenon will shape the future incidence of infectious diseases, unlike Reiter, who seems limited in his strict consideration of historical and entomological factors. However, an overwhelming majority of medical researchers find neither the arguments of Reiter nor Epstein rather convincing as a result of their narrow and exclusive viewpoints.

Most medical researchers acknowledge that arguments citing a causative relationship between climate change and the spread of mosquito-borne diseases are oversimplified because of their limited consideration of other confounding variables; in order to identify climate change’s true implications on human health, these researchers believe historical and current trends must be considered through an epidemiological lens. In his article, “Early effects of climate change: do they include changes in vector-borne disease?” R.S. Kovats, a lecturer on environmental epidemiology at the London School of Hygiene and Tropical Medicine, argues that “the observation that climate change is associated with changes in vectors or diseases does not, of itself, prove a causative relationship, since it is usually not possible to completely exclude all alternative explanations for any change in disease patterns” (Kovats, 2001). Confounding variables, which include globalization, land use, demographics, and human behavior, make it statistically erroneous to correlate mosquito-borne disease incidence directly to climate change; thus, Kovats believes climate change should be considered one of many factors influencing disease dynamics. Kovats argues that there is a lack of strong evidence of an impact of climate change on vector-borne diseases, further necessitating the need to conduct long-term studies analyzing the relationship between the two.

Although medical researchers have differing opinions regarding the impact of climate change on disease transmission, a majority agrees that there is a lack of concrete evidence to support a direct correlation between the two; such lack of evidence creates this debate. However, with medical researchers so heavily invested in such a passionate debate, the purpose of the debate is often buried within the argument itself and unclear at times. What is the purpose of researching the impact of climate change on the transmission of mosquito-borne diseases? Medical researchers believe scientific evidence of the relationship between the two will result in more effective preventative measures. However, the close relationship between climate change and other human-related factors, such as deforestation, urbanization, and water control projects, allows each of them to be treated as a single factor rather than multiple factors influencing mosquito-borne diseases. Thus, climate change’s effect on the spread mosquito-borne diseases is inherent within the human-related factors themselves.

**Outdated Solutions: The Concerning Outlook for Modern-Day Preventative Measures**

By isolating factors that play a role in influencing the dynamics of mosquito-borne diseases, medical researchers hope to develop preventative measures that will more effectively target such specific factors, thus minimizing global disease emergence. To develop these measures, researchers must identify the factors that influence disease emergence and determine how
to control such factors. Through this research, modified mosquito and virus control procedures can be developed to allow for the long-term treatments necessary to aid patients and prevent such diseases. Identifying the role of climate change, however, would not help in the development of control measures because of the close association between climate change and human behaviors; climate change should be treated as inseparable from individual human factors because of their interdependence. Indeed, many past eradication efforts have had little to do with the changing climate, yet many solutions have allowed for a reduction in mosquito-borne infections over the past century. However, the changing dynamics of these diseases have allowed for their resurgences, further necessitating the development of alternative solutions targeting the individual human factors contributing to the increased prevalence of mosquito-borne diseases.

The history of control strategies aimed at reducing the burden of mosquito-borne diseases provides important insights into current control strategies. For the past 120 years that mosquitoes have been identified as vectors responsible for the transmittance of various infectious diseases, medical researchers have been exploring the effectiveness of various preventative measures that can be traced back to the 1940s.

The discovery of DDT and the establishment of the World Health Organization defined a period of optimism that lasted from the late 1940s to the mid-1960s. The prevention and control of mosquito-borne diseases, more specifically malaria, became a central focus. Researchers were hopeful that “time-limited special-purpose campaigns, involving DDT spraying, chloroquine chemotherapy and active case surveillance, [would] achieve global eradication in a matter of years” (World Health Organization, 1999). The trend in vector-borne diseases quickly flipped over the course of a few years. For example, malaria had been nearly eliminated in Sri Lanka, with only 31 and 17 cases reported in 1962 and 1963, respectively (Gubler, 2010). The dramatic decrease in cases of malaria caused many nations to be hopeful of having the ability to “banish malaria completely from their borders” (World Health Organization, 1999). However, by 1967, 3,468 cases of malaria were reported in Sri Lanka, followed by a major epidemic of 440,644 cases the next year (Gubler, 2010). Virus resistance to DDT and concerns about its safety resulted in wavering support for such control strategies, quickly dwindling early optimism surrounding the premature idea of eradicating mosquito-borne diseases.

Following limited international funding for malaria control in the 1970s and 1980s, a revised global strategy approved by the World Health Organization in 1992 resulted in a greater emphasis placed on the importance of malaria control. Through focused research on the containment and control of malarial epidemics, scientists were able to develop a wide range of tools for malaria prevention. An insecticide-treated net is an example of such a tool that has become an increasingly popular preventative measure over the past 15 years. While “the use of treated bednets and curtains has led to reductions in child mortality ranging from 14% to 63% in African trials,” implementation remains limited and achieving high retreatment rates of nets has proved to be difficult (World Health Organization, 1999). Moreover, the perfection of insecticide-treated nets is not a comprehensive solution to disease outbreaks. Other current preventative measures include the use of drugs, early treatment, and residual house spraying of insecticides. However, these control strategies are limited in their effectiveness because of the distinct challenges facing each one. Although the use of drugs is a simple and cost-effective way to manage infectious diseases, the regulation of drug vendors presents an even bigger issue. Although access to early treatment of diseased individuals reduces the rate of malarial infection, it is economically unfeasible for many individuals of low socioeconomic status living in developing countries to get the good quality treatment they so critically need. Although house spraying of insecticides allows for the management of mosquito populations, its potential environmental and health effects in conjunction with its creation of resistant mosquito and virus populations make it a poor option. While many of these control strategies may provide temporary relief, they by no means represent a panacea.

As a result of the numerous drawbacks of current interventions, research should be focused on the development of nuanced preventative measures that target the human activities contributing to changing disease dynamics but do not ignore the possible influence of global climate change. By analyzing each factor’s close
relationship to climate change, solutions can be tailored to address each human-related factor influential to the spread of mosquito-borne diseases while inherently curbing the severity of climate change as well.

The Relationship Between Human Behaviors and Climate Change

Most voices in the debate echo that there are various human-related factors contributing to the increased incidence and distribution of mosquito-borne diseases. Since “there are a number of other significant social and environmental drivers of vector-borne disease transmission in addition to climate change,” (USGCRP) it is difficult to assess the extent to which climate change affects disease transmission. However, the relationship between climate change and the prevalence of mosquito-borne diseases will not alter the measures taken to control disease outbreaks because climate change is caused by the same human behaviors that have already been identified by medical researchers to contribute to the spread of infectious diseases.

In considering the relationship between climate change and mosquito-borne diseases, medical researchers agree that human activities on a more local scale have noticeable impacts on the dynamics of disease. For example, Paul Reiter cites numerous human activities and cultural and behavioral traits that affect disease transmission. Forest clearance, infrastructure projects, urbanization, and higher birth rates are a few of many human-related factors that contribute to the creation of excellent breeding sites for mosquitoes and the expansion of their physical habitable ranges. However, these same factors contribute to the phenomenon of human-induced climate change as well.

While many developing countries are forced to clear forests for the agricultural demands of their growing populations, such forest clearance releases sizeable amounts of carbon dioxide into the atmosphere and thus increases global temperatures. According to the World Carfree Network, deforestation is responsible for 15% of global carbon emissions (Scheer, 2012). When trees are cut down, they release the carbon they once stored into the atmosphere, where it reacts with oxygen to form carbon dioxide. Carbon dioxide, a greenhouse gas, traps heat and warms the Earth’s surface. Deforestation is only increasing; according to the Environmental Defense Fund, “Unless we change the present system that rewards forest destruction, forest clearing will put another 200 billion tons of carbon into the atmosphere in the coming decades” (Scheer, 2012). Global climate change will continue to worsen with increased rates of deforestation, and the incidence of mosquito-borne diseases should expect to increase as well.

Deforestation creates ideal conditions for mosquitoes to breed and spread their infectious diseases. For example, the epidemiology of malaria in the Amazon is being altered as “deforestation and land alteration facilitate environmental and climatic conditions that impact the ecology of mosquito habitats and create new places for water to accumulate” (Gottwalt, 2015). As a result, mosquitoes, which breed in undisturbed standing water, will have more area in which to breed, creating a larger mosquito population to spread the disease. Such altering ecosystem dynamics result in a strong, positive association between deforestation and the emergence of vector-borne diseases. Urbanization and population demographics, like deforestation, contribute to both climate change and the increased incidence of mosquito-borne diseases.

As the world’s population continues to expand and people are forced to settle in densely populated urban areas, the increased consumption of resources and use of fossil-fuels will contribute to the changing climate. Currently, the Earth has a human population of over 7.3 billion, according to the United Nations Department of Economics and Social Affairs. It is expected to reach nearly 10 billion people by 2050 (UN DESA, 2015). The continued population growth will force many to concentrate in urban areas as a result of the limited land available for such a rapidly growing population. In fact, globally, more than 54 percent of the world’s population resides in urban areas, and by 2050, 66 percent of the world’s population is expected to be urban (UN DESA, 2014). Climate change is largely influenced by this urban growth because “in order to keep up with rapid urban expansion and urban population growth, more resources as well as more consumption and production are required” (Sustainable Urban Futures, 2016). Since most of the “primary energy sources transformed to be available to most of the cities around the world are still fossil-based,” cities are responsible for more than 75% of greenhouse gas emissions, a trend that will intensify with
an increasing population (Sustainable Urban Futures, 2016). In addition to contributing to climate change, increasing urban populations result in a greater prevalence and distribution of mosquito-borne diseases.

Urbanization and changing population demographics increase the potential for mosquito-borne disease outbreaks by providing mosquitoes with human “hosts” to prey on. Nikhita Puthueveetil of the Virginia Commonwealth University argues that while “urbanization often destroys the habitat of the virus and its vector,” mosquito-borne viruses and their vectors are highly adaptable (Puthueveetil, 2016). Due to urbanization and an increase in the number of humans, some mosquito species become anthropophilic, preying specifically on humans rather than animals. Thus, urbanization often promotes both mosquito population growth and virus population growth. Likewise, urbanization and a growing population promote a greater need for resources. Water is an example of a resource that is vital for a growing population. Many urban cities rely on canals and dams for the transportation and storage of water. However, like urbanization itself, these water control projects contribute to climate change and the fluctuating dynamics of mosquito-borne diseases.

While small-scale water projects are meant to better society through the creation of infrastructure that will provide for local communities, they have become one of the largest sources of greenhouse gas emissions. Although water control projects, such as the creation of reservoirs, irrigation canals, and dams, are necessary for the transportation and storage of water in many communities around the world, these seemingly “small” water projects are major sources of climate-changing pollution. For example, according to Brazil’s National Institute of Space Research (INPE), “dams may be one of the single most important contributors to global warming, releasing 104 million metric tons of methane each year” (International Rivers, 2007). Thus, Ivan Lima and his colleagues from INPE imply that the world’s 52,000 large dams contribute more than 4% of the total warming impact of human activities and are the largest single source of human caused methane emissions. These infrastructure projects similarly contribute to the increased prevalence of infectious diseases.

Water control projects also expand the distribution of mosquito-borne diseases by providing breeding sites for mosquitoes. For example, “in the tropics, during construction of dams and canals, excavation pits provide breeding sites for mosquitoes where they lay buoyant egg masses” (Patz, 2000). Moreover, deeply shaded pools, seepages in forests, footprints, irrigation ditches, and excavated depressions in the open sunlight add to the possible areas mosquitoes can deposit their eggs. Water control projects provide plentiful habitats for mosquitoes to breed and thrive. Such a “wide variety of conditions under which at least a few species [of mosquitoes] are able to thrive ensures that parasitic disease is ubiquitous [and] flourishing throughout many regions of the world” (Patz, 2000). Deforestation, urbanization, and water control projects all promote the growth of infectious diseases by providing advantageous breeding sites for disease vectors. The interrelatedness of these human factors and climate change makes treating climate change as a separate influence to mosquito-borne diseases unnecessary.

**Umbrella Solutions: Climate Change’s Dependence on Local Human Activities**

While there is no single panacea to the potential outbreaks of mosquito-borne diseases, control strategies that directly address the influences of such human activities on disease dynamics will better prevent infections than a debate about the role of climate change. Climate change itself may alter the dynamics of mosquito-borne diseases; however, control strategies focused on addressing human interactions and activities will inherently account for climate change’s possible influence on mosquito-borne diseases. Thus, in prioritizing the development of preventative treatments that target specific contributing factors to infectious disease over research on climate change’s possible influence, medical researchers will better be able to limit disease transmission.

Integrated vector management (IVM) can reduce vector breeding grounds altogether through improved strategy design. Unlike popular preventative measures today, IVM does not rely on a single method of vector control. Rather, it “stresses the importance of first understanding the local vector ecology and local patterns of disease transmission, and then choosing
the appropriate vector control tools, from the range of options available” (World Health Organization). IVM requires health impact assessments of new infrastructure development, which includes water resources, irrigation and agriculture; such assessments will help researchers “identify potential impacts on vector-borne disease upstream of major policy decision so effective action may be taken” (World Health Organization). IVM’s environmental management strategies reduce vector breeding grounds through improved design and operation of water resources development projects and the use biological controls to target and kill mosquito larvae without generating the ecological impacts of chemical use. Thus, IVM is able to account for the local human activities that contribute to disease outbreaks. Like IVM, Integrated Pest Management focuses on seeking out control tactics customized for the factors influencing the prevalence of mosquito-borne diseases.

Integrated Pest Management’s (IPM) emphasis on habitat management and control of the immature stages of mosquito species reduces mosquito populations while minimizing the environmental impact of mosquito control measures. IPM can be described as “an ecologically based strategy that relies heavily on natural mortality factors and seeks out control tactics that are compatible with or disrupt these factors as little as possible” (Environmental Protection Agency). Similar to IVM, IPM considers the interaction between control practices, weather, and habitat biology before deciding on a course of action. Control strategies, such as IVM and IPM, will reduce the prevalence of mosquito-borne diseases through various mosquito control techniques that simultaneously limit adverse health and environmental effects.

**Conclusion**

While recognizing factors influential to the spread of mosquito-borne diseases is helpful in developing control strategies, medical researchers seem to sacrifice the development of preventative measures in order to focus on identifying the possible influence of climate change on vector-borne diseases. Medical researchers argue for the necessity of additional long-term research analyzing the correlation between climate change and mosquito-borne diseases in hopes of thus being able to tailor control strategies to target the influence climate change has. However, such time and resources are better spent creating more effective control strategies for mosquito-borne diseases because of the close association between climate change and other human factors. These interventions will inherently account for climate change's possible influence due to the strong correlation between the human actions responsible for disease transmission and climate change itself. Innovative control techniques will prove to be necessary in order to prevent and treat infectious disease outbreaks; however, to be of maximum effectiveness, individuals must learn to abstain from partaking in the activities promoting the spread of disease in the first place.

In order to prevent the spread of mosquito-borne diseases and the incidence of climate change in the first place, public education can serve as a powerful tool. Through public education, individuals can limit their carbon footprint and thus limit their influence on the spread of mosquito-borne diseases. There are many ways for ordinary individuals to limit their contributions to both global climate change and the spread of mosquito-borne diseases. For example, through recycling, going paperless, and eating vegetarian meals as often as possible, individuals will lessen the need for deforestation, thus reducing vector-breeding sites and the amount of greenhouse gases contributing to global climate change. Individual actions can be taken to address each human-related factor contributing to disease outbreaks.

Medical researchers must focus on developing improved preventative measures to control the resurgent mosquito populations responsible for spreading infectious diseases. When considering the global phenomenon of climate change and the biology of a mosquito, the importance of the two in this debate is obscured because of their relative sizes. Medical researchers focus on the process of climate change in hopes of preventing future disease outbreaks, but they should be more focused on how certain human activities affect the prevalence of disease-carrying mosquitoes. Once again, the deceiving size of a mosquito masks the potent capabilities of the “little fly.”
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The American Organ Crisis

Despite the recent surge in healthcare technologies and medical practice innovation, increasing rates of organ donation to meet the need for solid organ transplants remains one of the largest unsolved problems in the American health industry. The United Network for Organ Sharing (UNOS) lists the current number of candidates on the transplant wait list at 120,000,22 with that number steadily increasing each day. Unfortunately, the number of American donors is nowhere near the number of potential recipients, as a low 40% of Americans consent to organ donation after death.21 As a result, only 28,000 transplants are performed annually,23 and an average of 21 people die each day due to not receiving a vital organ.4 America's potential supply of viable organs shrinks even further when considering the overall weaker physical health of Americans; those who want to donate are more likely to have unhealthy organs due to the prevalence of obesity and other health issues.7 As researchers struggle to grow organs and tissues in vitro to increase America's viable organ supply, hospitals must look towards other means of procuring donations. One potential resource is a small percentage of Americans who no longer need their organs: those who have suffered from cardiac death.

First, a distinction must be drawn between the medical definitions of “brain death” and “cardiac death.” Candidates for both include patients with severe neurological injury (from stroke, trauma, anoxia, hemorrhaging), degenerative neuromuscular diseases, or end-stage cardiopulmonary diseases.2 Although both outcomes stem from severe brain injury, cardiac death does not meet the clinical standards for brain death. The concept of brain death evolved between 1902 and 1950. After brain death was defined, the organs used during transplantation could be more freshly harvested from brain dead organ donors. This led to overall more successful organ transplantations and brain death are now inextricably linked, and a diagnosis of brain death is used in the status quo to determine the appropriateness of organ transplantation for dead hospital patients. There are a variety of tests a physician can administer in order to diagnose brain death: brain stem reflex assessments, apnea tests, and coma appraisals that determine if a patient has truly passed.14 Examples of tests include searching for an absence of gag reflex, corneal reflex and cough reflex. Other tests look for high body temperature or lack of spontaneous respiratory effort. The time of brain death is marked as a patient’s legal time of death, and then donation after brain death (DBD) can occur.

In contrast, cardiac death, or non-heart-beating death, occurs when a patient cannot be legally declared dead due to lingering neurological activity, yet the patient has no chance of recovery. In this case, a physician must determine that the patient would die without life support, and the patient’s family must subsequently choose to end life support.24 Only then is donation after cardiac death (DCD) discussed with the patient’s family. A referral is made to an Organ Procurement Organization (OPO), which then determines the patient’s eligibility to be an organ donor. If a patient is suitably eligible to donate and the patient’s family gives consent, the patient is removed from life support and the donation process can begin.25 Although DCD could theoretically be as viable as DBD in determining a patient’s eligibility for donation after serious brain injury, many hospitals do not accept DCD organs as readily as DBD organs. This piece will now delve into the reasons why the American medical community has been wary of accepting DCD.

Surgical Benefits

The main surgical benefit behind DCD is that the patient’s body, through use of a ventilator, is still alive. One organ donor can save up to eight lives through donating 2 kidneys, the heart, 2 lung lobes, the liver, the small bowel, and the pancreas.28 In order to provide a patient with healthy organs, organ removal
must occur as quickly as possible to prevent the deprivation of oxygenated blood to the organs. Therefore, donated organs are most viable if transplanted soon after a patient’s death, but can be chilled in a preservation solution for a number of hours before becoming too damaged for transplant. The possible storage times range from less than 6 hours for a heart or lungs, less than 12 hours for a pancreas or liver, and less than 30 hours for a kidney.26 After deciding to go through with DCD, there are several hours to prepare for surgery without having to worry about the organs expiring, as the body is still alive while on ventilation. This removes the time crunch usually involved in quickly bringing in a transplant team and conducting the surgery for a DBD.

Aside from relaxing time constraints on organ preservation, DCD affects various preparatory processes that occur before donation. The National Protocol for Donation and Cardiac Death explains how the treatment for potential DCD donors differs from the treatment for those who are removed from ventilation without donation. Differences include delaying the withdrawal of ventilation to allow for the organ donation team to organize, taking blood samples from the patient to match organs to potential recipients, moving in a surgical team, and transferring the patient to a more suitable hospital space for the surgery. This process can take up to twelve hours, as it includes ample medical testing and information collection as well as organizing psychological support for the family.13 The extended process of DCD ensures that paperwork and organ matching can be done before the surgery, as opposed to the two being done concurrently.

**Implications for the American Donor Pool**

A 2011 study examined 1137 recipients of DCD donor organs over 28 years and found comparable patient and graft survival rates between DCD and DBD transplant recipients for the kidney, pancreas, and lung after 1, 3, and 10 years.1 Although there was a slightly higher risk of complication for DCD recipients, particularly for those who received livers,16 this study successfully demonstrated that kidney, pancreas, liver, and lung allografts from DCD donors were viable options for those on the waiting list. Currently, around 5% of donated organs in America come from DCD. Of the 2.2 million people who die each year from cardiac death, only 2% of them end up donating organs.3 In comparison, DBD contributes to roughly 92% of deceased organ donors in America,6 indicating that a similarly significant donor pool could be gathered from DCD if the practice became more widespread. Estimates show that more than 20,000 patients who die from cardiac death each year may be eligible to donate, potentially doubling the number of available DCD donors.27

Unfortunately, DCD was not considered a viable option for donation until recently, and therefore there are some systemic problems that the medical community must solve. First, DCD is not practiced widely enough to warrant the existence of a standard protocol. An OPO survey conducted in 2005 found that 92% of OPOs used a 5-minute interval from asystole to the declaration of death, consistent with recommendations from the Institute of Medicine. However, some OPOs used 4-minute or 2-minute intervals to determine death, presenting a wildly imprecise three-minute range used by American OPOs as a “standard” DCD protocol.2 There are additional problems with hospital transparency; in approximately 5% to 10% of cases, a patient may not expire within two hours of being taken off of life support,2 making their organs ineligible for donation. The National Protocol for Donation and Cardiac Death mentions that most patients die within 10 to 20 minutes but may take longer than two hours.13 It is unclear if families are made aware that there is a one in ten chance of a failed donation attempt. This means if a patient is assumed to be brain dead but fails some of the tests that check for brain death confirmation before organ donation, the patient is no longer classified as dead and needs additional medical attention. This stops the donation process. Families are re-consulted about patient outcomes and the patient is administered CPR and additional life support. In this situation, families are often alarmed that the patient’s original state of cardiac death was misdiagnosed, further tarnishing DCD’s reputation in the public eye. Ultimately, consent to donate in all situations relies on a favorable public opinion of the donation process, and the fear surrounding muddy definitions of cardiac death has led to many hospitals refusing to carry out the procedure.
Ethical Concerns

Within the medical community, the efficacy of cardiac death definitions and the dead donor rule (DDR) has come into question, particularly as America’s organ shortage leads to an increased focus on donation after cardiac death. There are some clear ethical benefits to donation after cardiac death: DCD increases the donor pool, saving the lives of people on the transplant waiting list, and allows providers to fulfill the wishes of patients who wished to donate but would not be eligible for donation under brain-death criteria. Unfortunately, despite these benefits, the majority of debate on donation after cardiac death has been on its ethical concerns.

Both brain death and cardiac death have been codified in the Uniform Determination of Death Act (UDDA) since 1981: “An individual who has sustained either (1) irreversible cessation of circulatory and respiratory functions, or (2) irreversible cessation of all functions of the entire brain, including the brain stem, is dead.” When combined with the DDR of organ transplantation, which states that vital organs can only be taken from those who are dead, removing organs from a brain dead donor with a “living” body becomes legally and ethically acceptable. Theoretically, these rules and regulations are in place to assuage the fears a patient’s family may have. Unfortunately, cardiac death is comprised of an even looser set of criteria than brain death, and many of the problems with brain death are present in cardiac death but at a greater degree. To start, many physicians disagree on whether a patient with some noncritical brain stem function can safely be declared dead. Even in the case of brain death, where there are 14 listed criteria that doctors can use to assess patients and an established recommendation of two examinations plus confirmatory testing with electroencephalography, which measures electrical activity in the brain. Standard protocol is rarely followed. A 2008 study from Pediatrics found that out of 277 brain-dead children in California, only one child received the recommended set of diagnostic tests. This same issue can easily be applied to cardiac death. The criteria for DCD are often up to the discretion of each individual hospital due to the lack of consensus across the medical community.

Unsurprisingly, one of the largest concerns with the concept of cardiac death is the fear that a patient is declared dead without a thorough attempt at saving his or her life. Patients worry that a physician may be so determined to help those that need organ donations, that they could unintentionally pressure a family to go through with DCD. Public concerns were raised in a 2006 case when a transplant surgeon allegedly administered fatal doses of morphine and lorazepam to a potential donor in order to hasten death. There is a paradox inherent in the field of transplantation: the need for a dead donor with a living body. Transplant surgeons are hyperaware of this issue; certain laws exist that rely heavily on semantics to distinguish between biological life and death.

In a 2011 paper, Robert Sade uncovers the rhetorical device within the DDR: the UDDA asks for an “irreversible” cessation of heart function, but if a physician has no intention of reviving a patient then the cessation of heart function is inherently irreversible. Along the same vein of thought, Don Marquis speaks on the reversibility of death in “Are DCD Donors Dead?” He notices, “If the transplanted heart functions in the recipient, then it was not dead when it was still in the donor. If the donor’s heart was not dead, then the donor should not have been pronounced dead on the basis of cardiac death.” Ultimately, he determines that DCD donors cannot be proven dead due to the inherent breaking of the dead donor rule upon the transplant surgery. He concludes that DCD should either be declared unethical due to violating the dead donor rule, or the dead donor rule must be fudged in some way to qualify a patient as rightfully dead. Clearly, even within the medical community there is ongoing debate about the ethics and potential liabilities behind allowing for donation after cardiac death.

This unclear definition of cardiac death is often the hardest part of the process for families to comprehend. Greater public education about DCD is needed, but considering that organ donation itself is a relatively new topic for the American public, the future in which all patients know about DCD and its nuances seems far off. Even brain death, which is defined far more concretely than cardiac death, is a difficult concept for patients and their families to grasp. According to Arthur Caplan of the NYU Langone Medical Center, “the term ‘life support’ exacerbates the
[lack of understanding about brain death] because those who are brain dead do not have a life to sustain." In the words of Nailah Winkfield, whose child was declared brain dead on life support, “I would probably need for my child’s heart to stop to show me that she was dead. Her heart is still beating, so there’s still life there.” Emergency medicine physician and bioethicist Aasim Padela clarifies this sentiment while speaking about brain death: “When you see someone who is in the hospital and has no cerebral function, that, I think is easier to accept as a situation where physicians may procure organs with consent.” But in the case of cardiac death, when patient still appears to have brain function such as temperature control or water and electrolyte balance, it becomes much more difficult to understand where the line between life and cardiac death lies.

Both the public and physicians appear uncertain about the placement of this life and cardiac death. A 2008 study “Survey of Pediatricians’ Opinions on Donation After Cardiac Death: Are the Donors Dead?” shows that after being given a description of a hospitalized potential DCD donor, most pediatrician respondents were not confident in answering whether the patient was dead and eligible to donate organs. From the evidence available that discusses concerns with DCD, it is no wonder that the practice is not widespread in America.

Weighing Outcomes

The 2005 case of Children’s Hospital in Boston gives a perfect summary of the challenges facing the normalization of DCD. The hospital gathered 17 doctors, lawyers, and health care professionals as part of a panel to debate the costs and benefits of allowing DCD, but were unable to come to a consensus even after two years of discussion. Supporters felt that the practice was legal and followed families’ wishes, but opponents worried that end-of-life care for critically ill patients could be compromised. There was a national conference about DCD in 2005 to address its ethical propriety. This debate has yet to come to a close, more than a decade later.

However, America has been making a slow shift towards accepting donation after cardiac death. The Institute of Medicine strongly endorsed DCD in order to increase the donor pool, and since 2007, The Joint Commission has required all hospitals to have DCD protocol for inpatients if they have the available facilities. That being said, fully fleshed-out DCD policies have yet to be fully implemented across a significant number of hospitals. Without a doubt, a more widespread practice of donation after cardiac death would improve America’s organ shortage, but first the current practice of donation after cardiac death must undergo further refinement. Without clarifying the conditions surrounding cardiac death to both physicians and the public, donation after cardiac death will remain on the ethical fence in the public eye. Luckily, America has the medical resources and technology to make donation after cardiac death safe, widespread, and beneficial to those on the waiting list. With greater education for patients and among medical providers, DCD will be on the way to gaining public trust and saving countless lives over the coming years.
References


The experience section presents public health challenges that students have encountered personally, highlighting the relevance of such issues to student life on a day-to-day basis.
I sit in a lab on the fourth floor of Herrin biology building, my fingers spouting codes. I press Enter and, within seconds, the map of global forest loss appears on my screen. The map looks like a night sky being observed from a lightless countryside. Red specks pepper the world, clusters delineating areas of especially intense deforestation. I press enter again and another map appears, but this time, it’s of Zika. Blue spots, signifying the infection rate, envelop the mountain ranges of Colombia in northern South America. These blue streaks often overlap with the clusters of red that mark mass deforestation.

As my eyes slowly scan the layers of digital images, my practiced mind races for clues of connections.

In the summer of 2015, Ixtlan de Juarez stretched out before my eyes; the lush carpet of oak trees rolled like tidal waves and I, still drunk with the aroma of deciduous flora, began rolling a transect tape methodically down the slope. I was in Oaxaca two years ago as part of a summer seminar led by professor Rodolfo Dirzo in the biology department. Nine other students and I were doing an ecological analysis of forest management. We set transects, counted oak
saplings, and calculated the rejuvenation rates of the oak forest that are being managed, hopefully in a sustainable manner, by the local logging companies. After I measured the diameter of the last sapling, I straightened my aching back and took one last look at the rich hills before me. Every extent of my view was a forest, except for occasional clearing of barren land: litmus strips of anthropogenic deforestation.

Nearing the end of my freshman year, I had no idea what I wanted to do during the upcoming summer. So I applied for random jobs and programs, in desperate hopes that any of them would accept me and my summer would not be wasted. Two programs accepted me. One took place in the tropical dry forests of Oaxaca, Mexico. The other was in downtown San Francisco. Never had I imagined before then that I would be forging an interest in the intersection of those two experiences.

About a month after the seminar in Oaxaca, I returned to Stanford for a Sophomore College called “AIDS Epidemic in San Francisco.” Instead of rolling tides of green oak forests, urban hill tops of rainbow-tattered crosswalks and narrow streets filled with angry cars and exuberant tourists produced a melancholic cacophony of human urgency. One night, we interviewed one the drag queens at a drag club. She tearfully recounted the memories of a dear friend who lost her battle to AIDS. The day after the interview, when we visited the National AIDS Memorial Grove, we found the friend’s name engraved on the sidewalk along with countless others. We bowed our heads in silence and I, who gave up counting the names, stared at another blatant display of loss.

It is difficult to trace diseases such as HIV back to their origins. It is commonly understood that HIV originated from apes and slowly spread across Africa. The first infected humans probably hunted infected chimpanzees for meat and came into contact with the virus-ridden blood. The first official case of infection dates back to 1959, just twenty years before the start of an epidemic that has now killed 35 million people.

Could these lives have been saved? What could we have done differently? As I continued to ponder these questions, I found myself drawing upon two of my vastly different experiences.

Forests of all types cover approximately 31 percent of the world’s land surface and provide important ecosystem services to us humans, including nutrient cycling, genetic resources, and even spiritual experiences. (World Bank, 2016) Unfortunately, we are rapidly cutting these forests down for agriculture, logging, and urban development. In 2016, the Brazilian government released an annual study that showed that the deforestation rate has increased by 29 percent since last year. (Butler, 2016)

Many scientists argue that destroying these forests are resulting in increased incidence of viruses (Norris, 2014). Barbara Han, a disease ecologist at the Cary Institute of Ecosystem Studies, uses an analogy of penetrating a balloon filled with viruses. “Whatever survives, spills out. Deforestation is closely tied to disease emergence.” (Doucelf, 2017)

In February of 2016, several months after the eventful summer, the World Health Organization declared an outbreak of Zika virus a Public Health Emergency of International Concern. Within months, the virus infected people all over Latin America. (Nebehay & Hirschler, 2016) To experienced epidemiologists, Zika
is just another emerging infectious disease. To me, it begged more questions. Why Latin America? How plausible would it be for the virus emergence to be related to the deforestation of the Amazon forests?

I brought my questions to professor Erin Mordecai, who studies vector-borne diseases and the effects of climate change. We ended up arranging a project for me to do the summer after my sophomore year. During those ten weeks, I made maps of the Zika epidemic and forest loss, performed spatial analysis on both, and discovered interesting interactions and possible connections between them. I learned that, although deforestation plays an important part in the patterns of Zika, its effects can be amplified when coupled with the variables of urbanization. In a way, urbanization is deforestation’s partner-in-crime.

Although at times I struggled with the technicalities of this project, I thoroughly enjoyed conducting research. The highlight of that summer was the poster session. A woman came up to me and told me she was from Colombia. She said her mother has dengue, another emerging infectious disease rampant in South America. As a native to Colombia and a daughter of someone with an infectious disease, she told me how concerned she was with the increasing numbers of people infected with diseases across the globe. “Your map captivates me,” she said. “It tells many stories like mine.”

As of November of 2016, Zika is no longer considered a global emergency. (McNeil, 2016) However, my work continues. As an Earth Systems major interested in spatial epidemiology, I am now preparing to write an honors thesis to continue studying how deforestation affects vector-borne diseases like Zika. Several people, intrigued by the interdisciplinary nature of my research project, have asked me, “How did you come up with this project?” To be frank, I do not believe I came up with it. Rather, the project, came to me when I decided to take chances on seeing the world from multiple perspectives.

Back in my lab, I continue fine-tuning the multi-layered map on my laptop. With a single stroke on the trackpad, my cursor can fly over Colombia, Oaxaca, and San Francisco, zooming into every street and peering into every coordinate. But I will never forget hugging the drag queen in San Francisco, tenderly caressing the young leaves of oak trees in Oaxaca, and seeking, with whatever I can offer, to protect the vulnerable.

References


On January 8th, 2017, in the small Northern Ontario community of the Wapekeka First Nation, twelve-year-old Jocelyn Winter took her own life. Two days later, another twelve-year-old, Chantel Fox, followed suit, and four other children were flown out of the remote community for emergency medical treatment. This is Canada in the 21st century, where suicide rates are five to seven times higher for First Nations youth than for non-Aboriginal youth, and where suicide rates among Inuit youth in Canada’s north are among the highest in the world, at 11 times the national average. This is Canada in the 21st century, where federal funding cycles are failing to budget for the preservation of Indigenous Life.

According to CBC News Thunder Bay, Health Canada, the department of the government of Canada with responsibility for national public health, received but was unable to fund a proposal from the Wapekeka First Nation to hire and train four mental health workers to help establish counseling sessions for young people identified in a suicide pact. Citing an inflexible system, Keith Conn, the regional executive for Ontario with the First Nation and Inuit Health Branch of Health Canada intimated that the proposal had come at an “awkward time” by which point all available funds had already been allocated. But for a people dispossessed of both their own sacred chronology and that of the state’s fiscal calendar, when is the right time?

Lisa Guenther would see this as a prime example of social death, whereby in a biopolitical sphere marginalized and multiply-marginalized populations are arranged to be deprived of moral purchase. The perniciously fiscal twist lies in the violent colonial mathematics that subvert Indigenous people into figures in an economic system that are subject solely to a state of fiscal time. As Billy-Ray Belcourt states in his essay, Meditations on reserve life, biosociality, and the taste of non-sovereignty, health is the “measure of a subject’s ability to adjust to structural pressures endemic to the affective life of settler colonialism.”

While Indigenous bodies are confined to reservations and in that sense “budgeted” out of a chance to build future worlds, the suicide crisis extends far beyond the Wapekeka First Nation into the public discourse around Indigenous health and survivance. This is not simply a public health crisis, and we have seen that coding it as such has done little for the communities, anyway. Worse even than the epistemic violence of misinterpreting and misrepresenting the experiences of Indigenous peoples within our Western discourse, we now invite them to the table to speak and commit a further ontological violence upon them (to take Spivak’s term to a conclusion amenable to the peri-colonial state in which we live) where the government interferes with the individual’s ontological and historical vocation to be more fully human. Therefore it shouldn’t be considered a stretch to say that in our present social conception Indigeneity is inextricably linked to a state of being “unwell” insofar as this radicalized crisis is at the convergence of two distinct geographies of reservation and statehood. We need to recognize this as a crisis of Indigeneous health, and to treat it as such through a lens that centers cultural safety and wellness. We need more than a framework, as our present solutions do not identify the necessary jurisdictional mandates or resources, responsibilities are not defined in a clear way, and there are no definitive timelines. Simply put, a framework does not have the sheer weight or power of an official strategy, but we need a more discursive politic if we are ever to address the social and colonial traumas as the heart of Canada’s Indigeneous suicide crisis and to rectify the dispossession.

Amber Dean’s Remembering Vancouver’s Disappeared Women: Settler Colonialism and the Difficulty of Inheritance, notes on page 20, that “critique is not equivalent to rejection or denunciation… the call to rethink something is not inherently treasonous but can actually be a way of caring for and even renewing the object in question.” Within the past two decades, community capacity building
and community empowerment have emerged from a critical space as key strategies for reducing health disparities and promoting public health.

The solution I would propose is threefold, comprising:

a) delivering culturally appropriate wellness programs

b) fostering greater collaboration between organizations to deliver services.

c) engaging scholars Diverse Indigenous scholars theorize material dispossession by the Canadian state, by capital, and by non-Indigenous peoples; deconstruct dehumanizing ideologies in popular Canadian media and academic writing; and describe and analyze Indigenous resilience (survival), resistance (decolonization), and resurgence (existential self-determination).

Indigenous Mental Health is a thing. Research into “evidenced-based, culturally relevant health practices that emerge from a constructionist framework rooted in Indigenous psychologies” is more needed than ever. Such practices would address the major themes of identity/self, historical trauma, cultural-specific mental health and well-being practices, cultural mistrust, empowerment, and political action. I propose therefore the SACRED method, which addresses issues of colonial oppression, considers the wishes and safety of community, and advances their own visions of self-determination and self-governance.

Sensitive: Many First peoples suffer not only from the proximal traumas of emotional, physical and sexual abuse and/or family violence but also from intergenerational trauma inherited via shared experiences of genocide, colonization, and alienation. Policy-makers must designate historical, inter-generational and racist incident-based trauma symptoms as legitimate trauma sequelae and do a better job of leadership in the areas of research and policy-making around acknowledging and healing historical trauma, of Indigenous and other oppressed peoples. Traditional, culturally-specific wellness practices must be validated and respected. Spiritual cleansing and rituals have deep histories in Indigenous cultures, and it is necessary to develop more reliable data regarding these practices, in rural and urban Indigenous populations.

Appropriate: Many First Nations peoples embrace a shared group identity whose substance is formed not just by one’s relationship to the community but also to the land and one’s ancestors, which includes plants, animals, and other natural elements that are under a particular nation’s guardianship. Thus, reduction or dispossession of land/loss of stewardship of one’s traditional plants and animals is experienced as an alienation or unmooring from the self, and in some communities is directly correlated with suicide. Please note that this is a tricky political proposition as Indigenous land dispossession is ongoing in many parts of the world, and restoration of the self theoretically would accompany Indigenous sovereignty.

Community-oriented: More efforts need to be put forward and supported to recruit more Indians, Alaska and Hawai'i Natives, First Nations, and global Indigenous who are better suited to serve their communities needs as researchers, educators, practitioners and policy-makers. Financial investment becomes key in empowering Indigenous people with the necessary tools to elucidate and develop evidence-based culturally relevant mental health constructs and paradigms that are community specific.

Responsive: We must put our money where our mouth is when it comes to Indigenous mental health. In times of crisis we must be responsive and listen to Indigenous people. They are best suited to report on their community and to propose solutions that will work for them. To be effective allies in mental health and wellness we must recognize the need for resources so that Indigenous communities may work towards a restoration of the self that would theoretically accompany Indigenous sovereignty.

Empathetic: Cultural mistrust is an issue that must be addressed. Indigenous peoples have suffered from colonized medical services for hundreds of years, from residential school horrors to forced sterilizations. For example, at a recent conference Inuit leaders reported they would not allow travel “south” (off the reservation) for medical care, due to past experiences where children disappeared and were never heard from again (as in the 1950’s tuberculosis epidemic in Canada) (Silversides, 2010). Any person wishing to
work with Indigenous communities must ensure they have received the proper training in cultural safety.

**Deliberate:** Any efforts to ally ourselves with Indigenous people must be deliberate in its stance for the dispossessed. We must support grassroots political movements that preserve and advance traditional values while orienting communities towards frameworks of wellness that allow them to dream of the future. We are not living in a post-colonial world, no matter what is said in academia, and we must use our education and our power to resist coloniality. This would be a primary prevention approach to Indigenous mental health issues — address them before they are created.

References


Lisa Guenther, Solitary Confinement: Social Death and its Afterlives (Minneapolis: University of Minnesota Press, 2013), xx

Since the time paper was first written, my brother has passed away of complications related to pneumonia. Macen Clay Holderman passed away at 2:45 p.m. on the 27th of September.

My Brother Macen

My brother Macen Clay Holderman was always a bit of a whiner, so nobody thought anything of it when he started complaining about a pain in his leg the early winter of 2014. It was probably just an excuse to skip soccer and play more Call of Duty with friends. Sure, this excuse had lasted a bit longer than others, but we reasoned his often complained about “growing pains” were nothing to worry about. After he had been limping for about a month, my concerned parents finally decided that this pain might be something more serious, perhaps a torn ligament. Their concern turned out to be justified.

Macen was diagnosed with osteosarcoma, an aggressive form of bone cancer, on April 15th of 2014 at Denver Children’s Hospital in Colorado. At the point of diagnosis, the cancerous, bony tumors, which originally started in the left knee, had spread to my brother’s lungs, and though his doctors saw little reason to quote what they referred to as ‘meaningless statistics,’ I looked up the survival rate for metastatic osteosarcoma on St. Jude’s Research Hospital’s website. His diagnosis carried about a 30% survival rate at 5 years (St. Jude, 1). The doctors at Denver Children’s explained that my brother and our family had a rough fight ahead of us. Treatments for my brother would involve five different types of chemotherapy, a modified amputation of his left leg known as a rotationplasty, a lung surgery known as a lobectomy, and an intermittent trip of almost 500 miles between Denver Children’s (where surgeries and new treatments would be performed) and our home in Albuquerque, New Mexico. Despite these challenges, my brother’s medical team was confident in Macen’s strength, and his ability to overcome this disease.

Treatment was hard on both my brother and the rest of our family. Through the next two years we would work to stay strong despite the constant fear, stress, and anxiety that my brother’s disease caused all of us. In the autumn of that year my brother had a rotationplasty performed to remove a tumor, and just a few months later Macen had two lobes of his lungs (and about 60 tumors) removed by surgeons in Denver. During treatment, my brother lost all of his hair, became increasingly weak and sick, and completely changed in personality. Some days, he was braver, stronger, and more compassionate than anyone else I have ever known. Other days he was reclusive and petulant, clearly exhausted by the tedious and painful treatments he was undergoing. For my part I began to drift away from my family, and
the better part of my senior year of high school was spent hiding away from my home in coffee shops, pretending my constant studying wasn’t some coping mechanism designed to hide my anxiety and growing dread from my siblings and parents.

**The Weight of Childhood Death**

The story of Macen and the rest of my family is far from unique. From genetic disorders to aggressive cancers, terminal pediatric illnesses and high mortality diseases affect thousands of children and their families every year. The CDC’s “National Vital Statistics Report” lists “congenital malformations, deformations and chromosomal abnormalities” as a leading cause of death for children under the age of 5, and childhood cancer as a leading cause of death for children between the ages of 5-18 (Xu, et al). For many of these diseases, curative treatments are not available, and patients have no or very little hope of recovery. Watching as a sibling or child suffers through these diseases and coming to terms with the fact that this loved one will likely die is a shattering and traumatic process. Terminal pediatric illnesses often leave many families unable to cope with the loss as siblings lose one of the closest emotional connections of their early lives and parents risk losing “basic aspects of a parent’s identity” (Edelstein qtd. in Buckle and Fleming, 1). Furthermore, parents may be unable to care competently for their other children, further increasing the burden on siblings of children with pediatric diseases.

What set my family’s story apart during my brother’s struggle with cancer was the immense support and care that we received from our church and local communities. Through a network of friends, churches, and relatives we received prayers, fundraising, and support from literally thousands of people. When a difficult treatment period arose, our church organized meals to be brought to our house. When my brother had trouble with stairs after his rotation-plasty, friends helped to build a bedroom on the first floor of our two-story house. When the family had to travel yet again to Denver, people donated us their spare airline miles and extra tickets. The outpouring of concrete support to my family was an amazing and constant wellspring of hope that pushed us through tough times, especially keeping my parents going as they fought for their son’s life.

Though, in general, support is available for most families dealing with high risk pediatric diseases, issues of the family are often rightfully dwarfed by weight of the patient’s own trauma. From groups of families struggling with similar illnesses I’ve learned that, while not unheard of, the level of support my family received from the point of my brother’s diagnosis onward is quite rare. Many families do not have the strong communities that my family relied on, a deficiency that can be quite damaging to families dealing with and recovering from pediatric illness. In the book, Family-Centered Psychosocial Care in Pediatric Oncology, authors and clinicians Lory Weiner and Maryland Pao discuss both the importance of the family in pediatric care and the lack of support often given to families in these critical situations. They argue that family members, especially siblings, experience many of the same psychological reactions to a cancer diagnosis as the patient does, and therefore need support for these symptoms (Weiner and Pao, 1). However, the current support for families dealing with high risk pediatric illness is generally insufficient for allowing families to heal, recover, and eventually thrive in the wake of devastating illnesses and the loss of a child. Distancing of families from support structures, a lack of consensus on therapies for family recovery, and the high visibility of the patient’s illness all culminate to negatively impact families experiencing the death of a child. To better serve these families, effective strategies for helping them
through their grief need to be developed, agreed upon, refined, and put into practice.

**Anticipatory Grieving**

In finding the best ways to guide families through their grief, it is helpful to delineate the pattern that grieving for a terminally ill loved one typically follows. In her book, *When a Brother or Sister Dies* Clair Berman, herself a survivor of the death of a sibling, summarizes the process of grieving as experienced by children she has interviewed. “They grieve when they learn of the condition, they grieve as the illness progresses and when the patient regresses they grieve anew when death claims its victim.” (31) Berman delineates here the difference between the grieving that happens before the death of a patient and the grieving that follows that death. In what she calls “anticipatory grieving,” Berman states that siblings and other family members “live in the shadow of death,” (32) constantly “bargaining” (32) for more time with their loved one while simultaneously and subconsciously making attempts to distance themselves from their loved one. These reactions to terminal illness present barriers to families trying to make the most of their remaining time with the patient, as well as to the ability of families to remain stable in the face of their loved one’s disease. These challenges include siblings’ inability to appreciate their own problems in light of the overwhelming “world of war” and “medical crisis” that is overtaking the lives of their brother or sister. As one surviving sibling remarked, the everyday, normal

A collage of people supporting my brother. Many of them are wearing T-shirts saying “Praying for Macen.”
struggles of her life were “just not up there on the list of priorities” (Berman, 34). As parents, extended family, and friends cluster around the affected child, siblings can feel increasingly marginalized, with serious deleterious effects to their academics, health, and their relationship with their siblings. With regards to academics, a study by Barbara L. Wolfe of the University of Wisconsin-Madison titled “School Outcomes of Chronically Ill Children and Their Siblings: A Multivariate Approach” found that, among other things, children with chronically ill siblings saw reductions in metrics like attendance, test scores, and even IQ over the course of their sibling’s illness (Wolfe, 6). The report hypothesizes that these effects are due to the reduced attention afforded to these children by their parents, who become more concerned about the illness their other child is battling (Wolfe, 11).

As someone who is currently experiencing the fallout of a terminally-ill sibling, and after reviewing interviews of many in the same position, it seems that almost nothing besides cursory grief counseling is being done to alleviate the effects that a terminally-ill child has on their siblings during the illness. Claire Berman recommends that extended family and close friends take time to discuss with siblings of terminally-ill patients the problems that they are going through, instead of the status of their brother or sister (35). She also advocates guiding children in developing identities outside of being a sibling to the dying child, such as recognizing their talents, or future aspirations. These social interventions could be suggested by medical care staff, religious leaders, or grief counselors, and when paired with traditional grief counseling (usually discussions about the process of grieving and the deceased) these measures could be simple and effective ways of guiding these children through the loss of their siblings.

A further supplement in assisting siblings of terminally ill children during their brother or sister’s illness is to provide financial or logistical help to parents of these children. Worries about planning trips to hospitals, family finances, and even things like cooking and cleaning can distract parents from taking proper care of their unaffected children. Organizations like the American Cancer Association, Relay for Life, and small community organizations such as local churches all currently offer these services. Along with this, options for respite care, professional care of an ill-patient that provides temporary respite for the primary caregiver, are both useful in allowing parents to spend time with their other children, and are provided by many non-profit and government organizations.

Cancer’s Reemergence

My brother had a lobectomy on the 14th of August, 2014, removing 65 tumors from his lungs. Though he was theoretically free of cancer at this point, he was kept on chemotherapy until March 18th to kill any small cancer cells that had managed to escape detection. After his treatment had ended, bone scans revealed that my brother was free from cancer, and we celebrated his new designation as being NED (a patient with No Evidence of the Disease). Although Osteosarcoma often comes back after this designation is given, we were hopeful that Macen’s battle with cancer was over, and we looked forward to his reintegration into school, and his continually growing proficiency with his prosthetic.

The return to normalcy, however, was not long lived. On December 6th, 2015, a little over a year from his lung surgery, a routine scan found four masses in my brother’s lungs. He quickly had the tumors removed in another lung surgery similar to the first, and was started on a clinical trial using immunotherapy to attack his tumors. After another bone scan showed continued growth of his tumors, my brother was removed from the trial. He is now undergoing chemotherapy and radiation therapy for tumors in his spine, arm, liver, and lungs. Although we remain hopeful for his recovery, the treatments remain effective, and his doctors have not classified him as terminal, I remain aware of the ever-growing odds against my brother’s survival.

When to Hope, and When to Plan

As a child’s illness progresses in severity, the issue arises as to the degree to which hope should be encouraged in parents and siblings. Hope is an important rallying tool, and hope for “beating the disease” can bring great strength to patients, care staff, and the family unit. However, unreasonable hope can prevent parents, caregivers, and siblings, for preparing properly, emotionally and logistically, for the worst-case scenario.

I currently face a similar dilemma with my brother Macen. There is no curative treatment option for
the extent to which his disease has manifested, and it is likely he will not live another five years. Though his illness is not terminal, and my family continues to keep hope alive, I constantly wonder if it is the right time to prepare myself for the worst, while simultaneously feeling fully the guilt of being unable to see his healing as a possibility.

This sentiment is echoed in the interactive piece That Dragon, Cancer a first-person exploration of the struggle of creators Ryan and Amy Green experienced as their son Joel struggled with, and eventually died from terminal brain cancer. Like my family, the Greens were and are deeply religious Christians, and like my family, they drew hope and comfort from their religious beliefs. Ryan and Amy faced a disagreement in facing Joel’s disease; Amy held hope until the end of Joel’s life that he would delivered miraculous healing by God, while Ryan demanded to feel fully the impending death of his child without the softening of groundless hope. While both parents maintained the overall hope that their son Joel would continue on to a better place in heaven (a belief that I happen to share about my own brother) which certainly brought a measure of comfort, Ryan rejected the tenuous hope for miracles in favor of dealing directly with the emotions of loss, whereas Amy clung to hope for healing as a support in Joel’s last days. The work as a whole acutely brings into perspective the ability for such hope to lend strength to families in times of need, and solidify a family narrative around a theme of hope, even while coming to terms with impending destruction.

Support for hope as a coping mechanism has been echoed in the medical community. The American Academy of Pediatric Practices official guidelines on Palliative care, outlined in the journal piece “Palliative Care for Children,” suggest that “continued hope for a cure, no matter how unlikely, may be an important coping mechanism” for parents and siblings dealing with pediatric terminal illness.1 Both Claire Berman in her book Losing a Brother or Sister and Jennifer Buckle and Stephen J. Fleming in their book Parenting After the Death of Child cite beliefs about the afterlife and religious beliefs in general as useful tools in dealing with the after effects of death. Generally, it seems that hopeful outlooks on the fates of deceased children should be encouraged, though there is not enough evidence to ascertain whether it is helpful for parents to hold out continued hope for miraculous healing regardless of the odds of their child’s recovery.

**Grieving After Death**

Arguable the most acute stage of grieving for a loved one is in the days and weeks directly after they have died. Family members, especially siblings of the deceased, can be aimless, emotionally unstable, and afraid for their own safety in the conclusion of a pediatric terminal illness. As an article from the National Child Traumatic Stress Network points out, children in these situations can even show reactions not easily recognizable as grief. “For example, a quiet toddler may have more tantrums, an active child may lose interest in things he or she used to do, or a studious teen may engage in risky behavior.” In addition to these personality disturbances, children may also develop a more intense reaction known as Childhood Traumatic Grief, defined by a pilot study as “A condition in which trauma symptoms impinge on the child’s ability to successfully address the normal tasks of grieving” (Cohen, 1). Though this disorder is not Post Traumatic Stress disorder, it does carry many of the same symptoms including, “reliving aspects of the person’s death,” “avoiding reminders of the death or of the person who died,” and “increased arousal and anxiety.”

Though feeling saddened and temporarily depressed by the loss of a loved one is normal in childhood, many children and teens do not have the ability to mentally or emotionally process the death of a sibling, especially as a result of terminal disease. If left unaddressed, problems resulting from this bereavement and ChildhooD Traumatic Grief can lead to children disassociating from their families, leaving communities that previously had offered them support, or becoming emotionally stunted as they grow to adulthood.

Currently most sibling grief after pediatric terminal illness is considered normal unless some visible problem manifests. When a sibling’s grief is recognized as problematic, interventions of traditional psychotherapy, such as mindfulness-based cognitive behavior therapy, are used to address problems of behavior, though often times other issues are written off or left untreated. Pilot studies, like the one conducted by researcher J. A. Cohens, have shown great
success using cognitive behavior therapy coupled with joint therapy sessions. These therapies involve both parents and their children, and can lead to significant improvement in the symptoms of childhood traumatic grief, as well as improvement in symptoms of anxiety and depression also present. In addition to these therapies, organizations like the National Child Traumatic Stress network recommend that parents talk often to their children about the deceased sibling, and monitor them carefully for the signs of Childhood Traumatic Grief mentioned above. It should be noted, as Jennifer Buckle and Steven J. Fleming write in their book Parenting after the Death of a Child, that parents may also enter a “numb survival” after the death of a child that can make this form of support difficult or impossible for them to provide (35). Monitoring the psychological health of the parents following the death of a child is also imperative to the health of their children. The number of siblings treated after the death of a child for Childhood Traumatic Grief must be expanded as caregivers, community members, and hospital staff become trained in better recognizing its symptoms, and more research needs to be done into the efficacies of certain psychological treatments in alleviating the symptoms of this disorder. Looking Forward and Moving on

After the initial pangs of loss set in following the death of a sibling, the greater challenge faced by survivors is learning to live without their brother or sister, but while keeping present their memory and legacy. In the aftermath of the death of a child, the entire structure of the family unit is tested. Roles that were filled by a departed sibling may fall to another child or be discarded (102-103 Buckle). Parents and siblings alike may feel that the deceased is being forgotten, or left behind by the family. This feeling of losing a connection with the deceased must be metered with a real and urgent need to move out of the shadow of grief and onward into life. At one extreme a family loses its identity as it tries to forget about the lost child, and at the other a family remains paralyzed by fear and loss, threatening the autonomy and function of the parents, and the emotional development of the siblings. Families must strike a healthy balance between these two poles to successfully overcome their grief.

Siblings themselves face a number of unique problems in the wake of losing their brother or sister. As noted in the article from the National Child Traumatic Stress Network, siblings can face “survivor’s guilt about being alive,” intense regrets about things they did or said to the deceased child, doubts about worldviews, and even personal and irrational blame for the death of their brother or sister. Moving forward children also must reformat their identity, both moving away from association with the deceased, and incorporating ideals and images that their sibling represented.

In the book, Parenting after the Death of a Child, Jennifer L. Buckle and Stephen J. Fleming argue that “picking up the pieces of the family requires regenerating the relationship with the deceased child in new terms” rather than simply moving on from it. Claire Berman, author of the book When a Brother or Sister Dies, similarly advocates that siblings and parents find ways to carry on the legacy of the deceased, such as organizing blood drives, scholarships, or charities in the name of their departed loved one (114). Berman also advises that families hold onto their deceased loved ones by making scrapbooks, mementos, and other “tangible connections” (113). In all Berman views the role of the mourning family not so much as to function without the deceased, but rather to incorporate the deceased’s goals and memory into their own lives.

As a society, we need to provide the guidance and resources children and families need to regenerate their relationships with the deceased. Grief counselors, medical staff, and community leaders need to incorporate remembrance ceremonies and guidance regarding legacy work in the name of the deceased child into the outreach they provide siblings and families, turning a tragedy into a lasting legacy that can keep the memory of the deceased child alive, and the relationship between the family and the deceased intact.

Bringing it Home

The question of how to revive a family following the death of a child is one that has been with humanity since before we were human. The family is the strongest unit of social cohesion, and while this lends it resiliency, it also means that its failures can impact each of the individual members of the family in a very serious way. For many, especially as we grow up, family forms the base unit of our identity, a constant place of love and security when it seems all
the world is a dangerous place, and because of that, death intrudes on the family in a way nothing else can. The death of a sibling shatters assumptions of belief, safety, and prosperity. It is an all-out assault on the identity of the sibling, on the identity of the parent, and on the idea that “everything will be all right.”

As a society and as a community, we owe it to ourselves and to each other to provide guidance and support through adversity as shattering as that provided by pediatric terminal illness. Those in the clergy and in other positions of leadership in the community have the duty to rally physical and emotional support to families in danger of collapse from these threats. Members of the medical community have a commitment to the health and wellbeing of their patients, and a duty towards monitoring and guiding the families of their patients comes with that commitment. Psychologists and counselors have a duty to listen to parents and siblings struggling with the grief before, during, and after the death of a child as well as a duty to provide guidance to those attempting to resolve the connections to their lost loved ones. As a society, as a larger family, we must provide the scaffolding and structure parents and siblings need to reconstruct, regenerate, and reform their lives in the wake of the pediatric illness. We must enable them to live.

References
Kim, Jew. The Holderman Family. 2014. Albuquerque, New Mexico. Digital Photograph

RESEARCH

The research section invites the members of the Stanford community to share their essays, perspectives, and research with a broader audience interested in public health.
Research Description and Goals

Psychiatry seems to be one of the few areas of medicine, perhaps the only one, in which treatments such as talk therapies, medication, and peer support are not well supported by more effective technological alternatives, such as ECT (electroconvulsive therapy), which alters brain functions with small, external electrical stimulations, or TMS (transcranial magnetic stimulation), which involves the use of a special electromagnetic device that sends short impulses to the brain. Often, diagnoses and therapies are left to the experience and subjective evaluation of the psychiatrist, whose accuracy is subject to constant criticism of other, skeptic psychiatrists with a different point of view. Conversely, technology nowadays is becoming more and more involved in the scientific community, leading research to solve modern and controversial topics. In the section Platelet's Fatty Acids and Differential Diagnosis of Major Depression and Bipolar Disorder through the Use of an Unsupervised Competitive-Learning Network Algorithm (SOM) of the article Open Journal of Depression, Serena Benedetti (et al.) discusses how, from a simple blood sample, it is possible to calculate the quantity of polyunsaturated fatty acids (lipids mostly found in seeds, nuts, or fish) that are present in the human body’s platelet membranes, which are small red blood cells that prevent bleeding. The research proposal is well-founded with the help of a mathematical analysis through a non-linear self-organizing map (SOM) that allows a better and more concise use of the information contained in the platelet. The combined application that the project proposes, therefore, could lead to an almost perfect diagnosis of the pathology afflicting the patient.

Project Significance

This is a huge step forward in the prevention of suicides and similar acts of self-harm, which affect not only a patient’s own health, but also that of others. Specialists in neurology or psychiatry, however, are less than welcoming to these studies. Instead of seeing these studies as a sign of progress in research, they treat them as untrue with everything to prove, since they see technology as a potential threat for their positions. It is not a mystery that in the near future, a functional, tested machine could give an almost perfect result, in which case the human voice will start to lose credibility and power. It is likely that managers would rather buy a new machine than hire a new employee. For this reason, even managers at the level of the Ministry of Health and other medical associations turn a deaf ear and do everything possible to silence these studies, hide their benefits, and hamper their development. It is crucial to keep in mind that a lot of diagnoses, when addressing cases of psychiatric disorders, are dubious at best, if not wrong. For instance, psychiatrists should not tell patients that their anxiety or depressive disorder are caused by a chemical imbalance in the brain when there is no evidence this exists. However, there are currently no other ways to improve the accuracy of these diagnoses, which is why these studies may be useful. It is unimaginable to think of being able to understand such a complex subject as that of the psychiatric pathology without having collaboration between various fields. In fact, this study is the first time that a case can distinguish between a bipolar patient and a depressed patient. The reason this distinction is relevant is because, as stated before, errors often made in the diagnosis of major depression versus that of bipolar disorder, are due to the delay in appearance of symptoms in the latter. Early on, the same patient who is diagnosed as a major depressed case is labeled as bipolar because there is no possible way to distinguish between the separate illnesses. After more than one hundred cases, it was possible to recognize that this kind of depression is characterized in a difference in composition of fatty acids in platelets compared to the one in subjects suffering from bipolar disorder. This is crucial to understanding that the individual does not change throughout life. Therefore, if someone who has major depression but
is misdiagnosed as a child and later said to have bipolar disorder, this someone won’t develop the bipolar disorder, but instead the major disorder would just get worse due to lack of appropriate therapeutics.

**Study Design, Part 1: Participants.**

In order to examine misdiagnoses in mental illness, psychiatrists scrutinized and recruited all volunteer participants, and patients underwent a semi-structured interview based on DSM-IV-TR criteria (Diagnostic and Statistical Manual of Mental Disorders, fifth edition). 132 total subjects were involved, 105 of which had either a bipolar disorder (BD) or a more generic mental disorder (MD), and 27 of which were completely healthy and represented the Control Group (CTR). The subjects were recruited without regard to sex, age, food intake patterns, or pharmacological therapies. Details are shown in Table 1 below:

<table>
<thead>
<tr>
<th>Subjects Investigated</th>
<th>Males</th>
<th>Females</th>
<th>Total</th>
<th>Average Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>MD</td>
<td>12</td>
<td>28</td>
<td>40</td>
<td>50.5 ± 14.7</td>
</tr>
<tr>
<td>BD</td>
<td>22</td>
<td>43</td>
<td>65</td>
<td>50.2 ± 13.1</td>
</tr>
<tr>
<td>CTR</td>
<td>17</td>
<td>10</td>
<td>27</td>
<td>***</td>
</tr>
</tbody>
</table>

**Table 1.** **CTR not included in calculations because considered as NOT-TREATED.*** CTR average age not available. Group matched for age, sex, and socio-cultural group to MD and BD subjects.

**Study Design, Part 2: Investigations.**

It is necessary to recognize the significant correlation between the biochemical mechanisms present in the blood and those existing in the brain—in particular in those brain areas most affected by the depression—so that the diagnosis of depression by the blood is reliable and a valid and essential diagnostic support to the clinic. Benedetti’s study examined the circulating platelets and posited that it could bring an innovative contribution to the psychiatric diagnosis with the introduction of a “biological marker of depression and bipolar disorder.” As a support of the diagnosis of the neuropsychiatric clinic, this study takes into account three fundamental scientific assumptions. The first is a new evaluation of the unique relationship of body and mind as a result of the discovery that many circulating cells, such as white blood cells and platelets, have the same receptors for the neurotransmitters that are present in neurons. Specifically, platelets and neurons have a very similar metabolism of serotonin. The second assumption is a new evaluation of the informational role of cell membranes. As highlighted in the research, subjects with depression present a different composition of fatty acids in platelets compared to those who suffer from bipolar disorder. Consequently, this different composition can modulate the responses to serotonin and antidepressant drugs. In support of the above-cited assumptions, the markers would allow a better understanding of the role of nutrition, inflammation and oxidative stress in the pathogenesis of depression.

The mathematical analysis the research is proposing, the SOM (Self Organizing Map), is a data visualization technique that reduces the dimensions of data through the use of artificial neural networks (ANN), and it is now needed to give a clearer picture of the above investigations. This particular algorithm allows you to view the results graphically by constructing a two-dimensional map that has the subjects analyzed in a continuous manner, not necessarily divided in specific categories or under strict criteria. This approach will evaluate the fatty acids of the platelet membranes of subjects diagnosed with Major Depression against a population control theoretically lacking this pathology.

**Study Design, Part 3: Procedures.**

1. Blood Sampling
2. Platelet Isolation
3. Platelet Membrane Fatty Acid Composition A
4. Mathematical Method:
   1. Self Organizing Map (SOM)
   2. On the Non-Manipulability of the SOM Built for the Classification of the Subjects
   3. B2 Index
   4. Plasma and Platelet Serotonin Levels
   5. Oxidative Stress and Inflammation Markers
   6. Statistics and Data Processing
Outcomes

After selection, 105 subjects were included. Among MD, 19 patients were on treatment with serotoninergic drugs, 10 with non-serotonergic and 11 received no therapy. Among BD, 28 patients were on treatment with serotoninergic drugs, 14 with non-serotonergic, and 23 received no therapy. The control group (CTR) comprised of 27 apparently healthy volunteers (M = 17, F = 10) matched for age, sex and socio-cultural condition to pathological subjects. The controls, assessed by a semi-structured psychiatric interview, were free of psychiatric illness or, at least, a psychiatric condition was not expressed. None of them were using anti-depressant therapy. The control group was selected among subjects with positive and negative B2 index (a simple mathematical tool used to establish degrees of viscosity and/or unsaturation within platelet membranes), without expression of psychopathology and without antidepressant assumption. In this way, researchers would be able to identify biomarker differences compared to drug treatment.

The SOM were administered with the values of the fatty acids of the two populations, mixing normal (healthy) and pathological individuals, and hiding all the information concerning their pathological state. The results obtained was that, using three particular fatty acids (Palmitic, Linoleic, and Arachidonic), the SOM has been able to construct a map of the two populations, recognizing as similar the subjects belonging to the same population and, at the same time, those different among the two populations.

The SOM interpretation consisted of the map shown in Figure 1. The subjects in red in the two intermediate areas (yellow and orange) have been interpreted as misdiagnoses of major depression. The SOM has demonstrated a great capacity of correlation in the diagnosis of major depression and, within the same diagnosis, has also revealed the existence of unambiguous, different biochemical characteristics of the fatty acids of the platelet. Nonetheless, the results are in accordance with the thesis that the diagnosis of major depression is often inaccurate and must be converted to a diagnosis of bipolar disorder.

Limitations

However, this research brings up an ethical issue. When we hear from the media about cases of murder, infanticide, uxoricide, or simple aggressions, they are often considered and defined as voluntary acts. Still, if the aforementioned blood tests were given to these individuals, a jury could not have the...
same level of confidence of the motives of the person who gave out the diagnosis, especially if there were no priors of mental conditions. In this case the acts of the convict would not be thought as voluntary and premeditated, but it might be classified as a consequence of the disease, therefore proving innocence. This means that a simple blood test can lead to an effective prevention of harsh sentences in a court of law, especially of borderline subjects, where the test could be the only solution to eventually justify their criminal act as involuntary.

Current psychiatrists are against this type of prevention, even if it would bring significant benefits to their patients through more accurate and precise diagnoses. In fact, some might object that this new diagnostic possibility could create discrimination in employment considering that the employer may require a negative test for his employees. However, in reality, there are no or few social repercussions. The “marker” is not evidence of the disease, but evidence of a predisposition to it, which can lead to prevention of the disorder.

Conclusion and future research

In conclusion, the experiment conducted tries to distinguish the disease at the first visit with the patient, so that the psychiatrist can better target the course of therapy because, at a certain point, treating a patient with major depression the same way as a patient with bipolar disorder is implausible. Due to physical-chemical characteristics in the neuronal membrane that are completely different between these two disorders, the same therapy may have devastating effects in one patient or the other. Kary Mullis, 1993 Nobel Prize in Chemistry, enthusiastically commented on the extraordinary importance of this research; in fact, this method may eventually allow the doctor to know if a patient has the intention to commit suicide, which is the leading cause of death in patients with bipolar disorder. In addition, an incorrect diagnosis and the wrong therapeutic intervention increase suicide risk by about 4 times. With developing research in this field, it seems that we are about to experience a tremendously promising turning point.

References


A Novel Inexpensive, Rapid, Simple, and Sensitive Aptamer-Based Sandwich Assay for Colorimetric Thrombin Biosensing
Jack Andraka*, Noor Siddiqui*, Sheetal Ramsurran

Abstract

In this paper, we report the development of an aptamer-based colorimetric assay for the inexpensive, rapid, simple, and sensitive detection and quantification of biomolecules based on the principle of sandwich ELISA. Thrombin was selected as a model analyte to validate the assay design, which involved the selective binding of one or two different protein epitopes with DNA aptamers. Two different substrates were employed: covalently modified cellulose and glass microscope slides, with the covalently modified cellulose immobilizing the target analyte via non-specific divinyl sulfone (DVS) chemistry while the glass microscope slide strategy utilized a physisorbed thrombin aptamer as a capture agent. The captured biomolecules were then labeled by iron oxide nanoparticle-aptamer conjugates, which was then visualized via the reduction of Cu2+ ions onto the surface of the nanoparticles. An electrophoresis mobility shift assay and agarose gel electrophoresis were used to confirm the aptamer-thrombin binding and aptamer-nanoparticle conjugation, respectively. The formation of the copper film on the iron oxide nanoparticles was then modeled via a nucleation-catalytic growth model in order to optimize the assay run time. Both sensor formats had a high sensitivity with the cellulose-based assay having an limit of detection (LOD) of 50 pM whereas the glass-based assay demonstrated a higher sensitivity with an LOD of 20 pM. In addition, the sensors demonstrated high specificity to thrombin with no significant signal being elicited from exposure to Bovine-Serum Albumin (BSA). The cellulose-based assay had a material cost of $0.10 and took 15 minutes to run, representing a 60 times improvement in cost and a 16 times improvement in time when compared to the gold-standard for protein detection, ELISA. Thus, the developed assay represents an inexpensive, rapid, simple, sensitive, and versatile method for the detection of biomolecules for a host of applications from diagnostics to biodefense.

Introduction

The detection of biomolecules (proteins, DNA, RNA) provides valuable information for a broad array of applications including clinical diagnostics, environmental analysis, food safety, and biodefense [Wang et al. 2013]. However, current methods for the detection of proteins rely heavily on antibody-based immunoassays such as ELISA, Western blot, and lateral flow and generally require timely sample processing, expensive and complicated laboratory equipment, and highly trained technicians [Shafee et al 2015]. As a result, the global health and biomedical communities have identified an urgent need for inexpensive, rapid, simple, and sensitive diagnostics for use in developing countries where the burden of infectious disease is highest.

Aptamers are single stranded oligonucleotides that selectively bind to various molecular targets, such as small molecules, proteins, nucleic acids, cells, or microorganisms [Song et al 2012]. Aptamers have a multitude of advantages over other biorecognition agents in bioassays due to their low cost, reproducibility, ease of isolation, reversible denaturing, good stability, and easy modification at virtually any desired site without loss of activity [Zhou et al 2014]. A variety of aptamer-based protein detection strategies have been described over the past few years, with approaches including fluorescence [Li et al 2014], electrochemistry [Jo et al 2015], inductively coupled plasma mass spectrometry [Ahn et al 2010], surface plasmon resonance [Cennamo et al 2015], and piezoelectrics [Neves et al 2015], yielding variable limits of detection, ranging from nanomolar to picomolar. However, many of these assays suffer from the same obstacles as their antibody counterparts, with test requiring timely sample processing, expensive and complicated laboratory equipment, and highly trained technicians, making these approaches ill-suited for resource-limited settings. In order to obviate
these difficulties, an aptamer-based biosensor was developed that combined the advantages of specific and sensitive detection of analytes found in immunoassays with the low cost and simplicity of optical readouts. The proposed assay utilizes either divinyl sulfone (DVS)-activated cellulose or aptamers physisorbed to glass microscope slides to immobilize a target biomolecule onto a solid substrate. The biomolecule is then labeled using aptamer-iron oxide nanoparticle conjugates and subsequently visualized by the reduction of Cu2+ ions onto the nanoparticles, which produces a visible color change that can be read by the naked eye or digital camera/cell phone camera.

As a proof of concept, thrombin, a serine protease involved in the last step of the coagulation cascade [Fenton et al 1981; Shuman et al 1986], was selected as a target molecule to assess the sensitivity and specificity of the developed assay. Thrombin is characterized by two distinct exosites, one binding fibrinogen (fibrinogen binding domain FBD) and the other binding heparin (heparin binding domain HBD) [Fenton et al 1981]. Two aptamers with high sensitivity and selectivity have been utilized for thrombin detection: TBA1, a 15-base pair DNA aptamer able to bind FBD and TBA2, a 29-base pair DNA aptamer able to recognize HBD [Meneghello et al 2012]. The concentration of thrombin in blood varies considerably: it can be almost absent in the blood of healthy subjects but can reach low-micromolar concentrations during the coagulation process [Shulman et al 1976]. In addition to its direct actions on the coagulation system, thrombin also functions as a potent signaling molecule that regulates physiologic and pathogenic responses. Thus, the developed biosensor for thrombin detection has potential for important clinical diagnostics as well as applications spanning from biodefense to environmental monitoring by altering the immobilization and detection aptamers.

Materials and Methods

Chemicals and Supplies

Unless otherwise stated, all chemicals were of analytical grade and obtained from Sigma Chemical Co. (St. Louis, MO). The sequence of the unmodified 15-mer TBA1 aptamer was: 5’-GGT TGG TGT GGT TGG-3’ and had a 5’-biotin modification to enable the conjugation of TBA1 aptamer to streptavidin coated iron oxide nanoparticles. The sequence of the unmodified 29-mer TBA2 aptamer was 5’-AGT CCG TGG TAG GGC AGG TTG GGG TGA CT-3’. All aptamers were synthesized by Thermo Fisher Scientific Co. (Waltham, Massachusetts), aliquoted to 10 µM, and stored at 4°C in TE buffer (10 mM Tris-HCl, 1mM EDTA) at a pH of 8.0. Human α-thrombin was purchased from Sigma Aldrich (St. Louis, MO) and dissolved in deionized water, aliquoted, and stored as recommended by the supplier. Streptavidin coated iron oxide nanoparticles were purchased from Nanocs Inc (Boston, Massachusetts) and stored at 4°C in 1x PBS (phosphate-buffered saline).

Electrophoresis Mobility Shift Assay Analysis for Binary Complexes

The binding of the two aptamers to the target analyte in solution was analyzed by an electrophoresis mobility shift assay (EMSA). Prior to incubation with thrombin, all aptamer samples (10 µM of oligonucleotide in a 100mM solution of KCl) were slow annealed by denaturing at 95°C and left to cool to room temperature. The folded aptamers were then diluted to 1 nM in TE buffer and then incubated with increasing concentrations (from 0 to 50 nM) of human thrombin in a total volume of 20 µL, at 25°C for 30 min. After incubation, the solutions containing free aptamer and thrombin-aptamer binary complexes were resolved by 12% non-denaturing polyacrylamide gels containing 1x TBE buffer (Tris-HCl 89 mM, borate 89 mM, EDTA 2 mM) and KCl 10 mM. The results of the assay were visualized with the fluorescent DNA binding dye Sybr Green II (Thermo Fisher Scientific), which preferentially binds to single-stranded DNA and emits fluorescence (excitement wavelength 488 nm, emission wavelength 522 nm) when bound to DNA. The fluorescence in the gels was detected via a Geliance 600 Imaging System (PerkinElmer).

Electrophoresis Mobility Supershift Assay Analysis for Ternary Complexes

To confirm the binding of the TBA1 and TBA2 aptamers to two distinct epitopes on thrombin to form an aptamer sandwich, a Supershift assay was utilized.
Both pairs of slow annealed aptamers (each 1 nM) were incubated simultaneously with the protein (5 nM) in a custom made binding buffer (Tris 20 mM, KCl 5 mM, NaCl 140 mM, MgCl2 1 mM, pH 7.5) in a total volume of 20µL, at 25°C for 30 min. Additionally, solutions of TBA1-thrombin and TBA2-thrombin binary complexes were prepared as described above. After incubation, solutions of free aptamers, binary complexes, and ternary complexes were also resolved by 12% non-denaturing polyacrylamide gels containing 1x TBE buffer (Tris-HCl 89 mM, borate 89 mM, EDTA 2 mM) and KCl 10 mM. The results of the assay were visualized with the fluorescent DNA binding dye Sybr Green II (Thermo Fisher Scientific), which preferentially binds to single-stranded DNA and emits fluorescence (excitation wavelength 488 nm, emission wavelength 522 nm) when bound to DNA. The fluorescence in the gels was detected via a Geliance 600 Imaging System (PerkinElmer).

Conjugation of Aptamers to Iron Oxide Nanoparticles and Confirmation via Agarose Gel Electrophoresis

TBA1 aptamers were purchased with a 5'-biotin modification and then conjugated to streptavidin coated iron oxide nanoparticles via biotin-streptavidin binding chemistry. To do this 100µL of TBA1 aptamers at a concentration of 1 µM was mixed with 100µL of 2 µg/mL of iron oxide nanoparticles and incubated at room temperature for 30 minutes. Unreacted aptamer was removed using centrifugal filtration five times at 3,000 rpm ( ). Gel electrophoresis was then carried out on 2% agarose gels with four samples: a 50 base-pair ladder, free TBA1 aptamer, aptamer-nanoparticle conjugates, and non-functionalized nanoparticles. The samples were then incubated in SYBR SAFE solution for 20 minutes and visualized under UV illumination (262 nm) by a Gel Doc XR+ Imaging System (BioRad). Zeta potential and particle size were calculated using dynamic light scattering (DLS) spectrophotometry (Zetasizer ZSP) at 25°C. Latex nanoparticles were used for calibration.

Preparation of Cellulose- and Glass-based Biosensors

DVS Activation of Cellulose

Physical adsorption is the simplest strategy for biomolecule immobilization onto solid substrates, with the immobilization of proteins onto supports such as polyvinilidene difluoride and nitrocellulose being well documented [Towbin et al 1979; Bode et al 1984; Tovey et al 1989]. However, these two substrates are limited in their ability to bind certain classes of biomolecules and are generally deficient towards the capture of nucleic acids, carbohydrates, and other small molecules, which limits their applicability in several important applications. To alleviate this issue chromatography paper was activated with divinyl sulfone (DVS), which would non-specifically immobilize molecules form a sample onto the cellulose (see Figure 1). This approach would reduce the material cost and complexity of the assay but would sacrifice some sensitivity and specificity due to the non-specific immobilization strategy.

A 10% DVS (v/v, 0.1 M sodium carbonate, pH 11) solution was used to activate cellulose membranes chemically. Chr 1. Chromotography paper (Whatman, 12.0 x 9.0 cm2 sheets) were immersed in 20 mL of 10% DVS solution and incubated in separate 400-mL-capacity plastic zip lock bags and agitated for 2 hours on a rocking shaker. The activated cellulose was then removed from the bags, rinsed three times in a plastic tray with 100 mL of deionized water, and then dried for 2 hours under ambient conditions. The activated cellulose could be stored by placing in aluminum foil under ambient conditions to shield them from light and dust.
Physisorption of TBA2 to Glass Microscope Slides

The glass microscope slide assay employed physiosorbed TBA2 aptamer to immobilize human thrombin to the surface, which was then labeled using the aptamer-iron oxide nanoparticles. This approach increased the sensitivity and specificity of the assay due to the specific immobilization strategy but suffered from an increased material cost and complexity of creating the assay. Direct physisorption of the aptamers to the surface worked well with the concentration for physisorption being 15 µg/mL. 200 µL of the aptamer solution was pipetted directly onto the glass slide and after physisorption of the aptamers for 1 hour in a humid chamber at room temperature, each detection zone was washed with 1 x PBS and then the entire slide was washed with deionized water. The biosensors were then either run immediately or stored in a dry chamber at 4°C.

Colorimetric Sandwich Aptamer Assays

Serial dilutions of human thrombin were created in deionized water at concentrations between 1 pM and 1µM. These samples were then used to create calibration curves for the biosensors to determine their limit of detection (LOD). Additionally, a sample of 10 µM BSA was used to assess the specificity of the assay.

Cellulose-Based Assay

The cellulose-based assay was run by first directly pipetting 20 µL of the sample onto the DVS-activated cellulose and incubating for 3 minutes in a sterile petri dish at room temperature. Following this exposure, the paper was dipped in a 2% milk solution (obtained using dehydrated milk reconstituted with deionized water) and incubated in a sterile petri dish at room temperature for 2 minutes in order to block the membrane from reacting with the aptamer-iron oxide nanoparticle conjugates. After this the cellulose was washed three times with 1xPBS solution and then incubated with 20 µL of 1 µg/mL of the aptamer-iron oxide nanoparticle conjugate solution for 5 minutes in a sterile petri dish at room temperature. The cellulose was then washed three times with 1xPBS solution and 20 µL of 1 mM CuSO4 solution was pipetted onto the detection zone and incubated for 5 minutes in a sterile petri dish at room temperature in order to visualize the assay results.

Data acquisition and processing

A digital camera with manual exposure settings (Nikon D1X) and a 1W white-light lamp (RadioShack) were attached to a stand so that they were the same distance away from the biosensors for each picture taken (see Figure 2) to ensure that all pictures have the exact same exposure so that measurements can be compared across assays. The measurement room was kept as dark as possible to prevent interference by room light, which could impact the exposure. All photographs were taken with a lens aperture of f5.6, a film speed of ISO 400, and a one second exposure time. The white-light lamp was warmed up for five minutes prior to taking a measurement and the assays were placed such that the entire substrate was in the camera’s field of view. The sensors were photographed before and after copper reduction to set a baseline measurement to compare the end results to in order to establish absolute colorimetric change.

The photographs were then analyzed using the histogram tool in the blue-channel to quantitatively measure the color change and the final absorbance (A) was calculated according to the equation: A = − log(I/I₀), where I is the measurement prior to copper reduction while I₀ is the measurement after copper reduction.

Modeling of Copper Film Formation

The extent of copper reduction under a range of surface iron oxide density and copper development time was predicted in order to minimize total assay time. To guide model development (creating...
a general mechanism and determining best-fit values of kinetic parameters – rate constants), a simplified experimental system of physisorbing different amounts of capture aptamers on the glass slide was used to produce a spectrum of surface iron oxide densities. This was achieved by adding varying concentrations of BSA as a competitor for physisorption on the glass microscope slide, with functionalization of a detection zone with a particular ratio of aptamers to BSA being done using an adapted procedure from Wild 2001. All tests were run as described previously with a thrombin concentration of 10 nM; however, colorimetric readings of the detection zone were taken every second during copper reduction to generate absorbance curves over time.

Results and Discussion

**Thrombin Recognition by Biotin-Modified TBA1 and TBA2**

**EMSA Analysis of Binary Complexes**

The results show that starting from a 2:1 ratio of thrombin to aptamer, the band of free aptamer gradually disappears as thrombin concentration increases while the band with greater molecular weight (lower mobility), corresponding to the TBA1-thrombin binary complex simultaneously appears (Figure 3, left). Thus, the results indicate that the biotin modification does not significantly impair the TBA1 thrombin binding. A similar assay was conducted with the TBA2 aptamer to confirm TBA2-thrombin binding. However, it appeared that the TBA2 aptamer was less sensitive than reported in the literature, implying potential error in the slow annealing for this aptamer or a faulty product (unlikely). Starting from a 10:1 ratio of thrombin to aptamer, the band of free aptamer also gradually disappears as thrombin concentration increases while the band of TBA2-thrombin binary complexes appears (Figure 3, right). An additional lane of 100 nM of thrombin was run for this binding interaction in order to better visualize the binding trend. Additionally, a decreased intensity of fluorescence signal for the TBA2 aptamer may also indicate a lower binding affinity between the indicator dye and the aptamer.

**EMSA Analysis of Ternary Complexes**

The results of the experiment indicate that the thrombin incubated with both aptamers was super-shifted, exhibiting a lower electrophoretic mobility than the binary complex, which is consistent with the formation of the ternary complex.

**Confirmation of Aptamer-Iron Oxide Nanoparticle Conjugates**

Conjugation of the 5’-biotin modified TBA1 aptamer with streptavidin coated iron oxide nanoparticles,
via biotin-streptavidin binding, successfully yielded aptamer-nanoparticle conjugates and led to an increase in both size (25.8±1.3 to 29.4±1.7 nm) and zeta-potential (-32.0±1.6 to -39.1±2.6 mV) of the nanoparticles. The conjugation of the TBA1 aptamer to the iron oxide nanoparticles was confirmed using agarose gel electrophoresis (Figure 5) with the free TBA1 aptamer matching the 15-bp band in the 50-bp ladder, and the aptamer-nanoparticle conjugate lane showing a band at a much higher molecular weight, confirming the conjugation of the aptamers to the nanoparticles. In addition, the spin filter purification successfully removed the free, unreacted aptamer from solution, thus preventing the potential reaction of free aptamers with bound thrombin.

**Modeling of Copper Film Formation**

The kinetics of copper reduction onto the iron oxide nanoparticles revealed a sigmoid-shaped response (Figure 6c), with the presence of an induction period, followed by the rapid growth of colorimetric signal and termination of signal growth. For curve fitting, a variation of the four parameter equation was used:

\[
A = A_{\text{min}} + \frac{A_{\text{max}}-A_{\text{min}}}{1+e^{\left(t-t_{A,\text{mid}}\right)/a}}
\]

Where \(A, A_{\text{min}}, A_{\text{max}}\) are the absorbance, minimum, and maximum values respectively, \(t\) is the time of copper reduction and \(t_{A,\text{mid}}\) is the time at the point of inflection, and \(a\) is a curvature parameter (Figure 6a). Curve fitting was performed using GraphPad Prism 6 software for nonlinear regressions. R-squared values for best-fit curves were 0.92 (aptamer only), 0.99 (1:1 aptamer:BSA), 0.99 (1:2), 0.96 (1:4), 0.96 (1:8), and 0.71 (BSA only).

The copper reduction onto the iron oxide nanoparticles is believed to start with the catalytic formation of in situ copper nanoclusters [Sia et al 2004; Masnadi et al 2015] around iron oxide nanoparticles and undergo a general mechanism involving a nucleation step [Wedgren et al 2003; Nyugen et al 2014] followed by an autocatalytic surface-growth step [Besson et al 2005; Watzky et al 1997]. It was also predicted that the mecha-
anism for signal growth termination was reduced copper deposition due to agglomeration of nanoclusters to catalytically-inactive bulk metallic copper.

\[ Cu(II) \rightarrow Cu(0) \quad k_1 \text{ nucleation} \]

\[ Cu(II) + Cu(0) \rightarrow 2Cu(0) \quad k_2 \text{ autocatalytic growth} \]

The model focused on the first five minutes of copper reduction as during this period a sufficient signal is generated and both the nucleation and autocatalytic growth steps are present (Figure 6c). The model assumes irreversible reactions, fast adsorption of reactants onto the iron oxide surface, even distribution of iron oxide density across the detection zone, and negligible copper precipitate desorption. Based on these two reaction mechanisms, the following equation was created for copper reduction:

\[
\frac{d}{dt}[Cu(0)] = k_1 S_{Fe}[Cu(II)] + k_2[Cu(II)][Cu(0)]
\]

With the \( k_1 \) being the rate constant of nucleation, \( k_2 \) being the rate constant of autocatalytic growth, and \( S_{Fe} \) being the surface density of iron oxide (expressed in moles of iron oxide nanoparticles per square meter of substrate). As the reaction progresses the number of active catalytic sites on the nanoparticles decrease due to the attachment of copper precipitate to the nanoparticles. As a result, \( S_{Fe} \) is expressed as a function of initial iron oxide surface density bound \( (S_{Fe, I}) \) and the extent of the nucleation reaction, \( \delta \):

\[ S_{Fe} = S_{Fe, I}(1 - \delta) \]

To estimate \( S_{Fe, I} \), the model assumed equal rates of physisorption between aptamer and BSA, a surface density of 0.5 \( \mu g/cm^2 \) of aptamer for aptamer-only experimental conditions [Wild 2001], a 1:1 capture ratio of thrombin to physisorbed TBA2, and a 1:1 labeling ratio of thrombin to TBA1-nanoparticle conjugate. To relate the amount of captured thrombin with \( S_{Fe, I} \), an average iron oxide nanoparticle diameter of 25.8 nm was used (obtained from DLS measurements):

\[ S_{Fe, I} = f_{Apt} \times 3.3 \times 10^{-8} \]

Where \( f_{Apt} \) is the percentage of aptamer to BSA in the physisorption solution. To estimate \( \delta \), a time \( t_n \) was defined beyond which negligible copper reduction occurs from nucleation on iron nanoparticles (since all surfaces of nanoparticles are already covered by reduced copper). This time was calculated by finding the intersection between the lines tangent to the best-fit curve of reduced copper formation at \( t_A, \text{mid} \) and \( t = 0 \) (Figure 6a). The active catalytic surface area was then expressed as

\[ S_{Fe, I} = S_{Fe, f}(1 - \frac{1}{k}) \]

The dependence of \( t_n \) on iron oxide nanoparticle density immobilized on the sensor surface by the aptamer sandwich interaction is shown in Figure 3b, and this relationship is generalized by an exponential decay fit:

\[ S_{Fe} = S_{Fe, I}(1 - \frac{4}{t_n}) \]

Where \( t_{n, max}, t_{n, min} \) are \( t_n \) at aptamer only and 1:8 aptamer to BSA surface coverage with \( k \) as a curvature parameter. The R-squared value of this fit was 0.97.

The developed model was then improved by comparing model predictions with the experimental data obtained for five different iron oxide concentrations. The two rate constants were determined via minimization of model error, which was performed using the pattern search algorithm (Direct search toolbox, Matlab) since this method handles the constrained nonlinear optimization problems in a short timeframe and does not require the function to be differentiable and continuous. By minimizing the objective function, the nucleation rate constant \( (k_1) \) and the autocatalytic growth rate constant \( (k_2) \) were determined to be \( 10^{-6} \text{s}^{-1} \) and \( 20 \text{m}^3\text{mol}^{-1}\text{s}^{-1} \), respectively (\( \text{m}^3 \) appears in the second rate constant due to the use of density measurements). To determine the goodness of fit between the model and the experimental results, the objective function was normalized by the total integral of the experimental curves over the five iron oxide concentrations (Figure 6d). The difference between the models predictions and the experimental results was found to be 9.2%.
Development of Colorimetric Sandwich Aptamer Assay for Thrombin

The aptamer-coated glass microscope slides and DVS-activated cellulose were employed as solid substrates for the immobilization of thrombin as well as the formation of the aptamer sandwich for the colorimetric detection of thrombin. A thrombin calibration curve was constructed for both assay formats using serial dilutions of thrombin in deionized water and measuring the resulting color change using a digital camera in conjunction with Adobe Photoshop. Overall, the analytical capacity of both sensors for the detection of thrombin exceeded expectations with limits of detection of 10 pM (glass-based assay) and 20 pM (cellulose-based assay), while demonstrating a wide detection range (10 pM-200 nM for glass and 20 pM-1 nM for cellulose). Additionally, the glass-based assay demonstrated no response in the presence of 1 x BSA as a negative control and the activated cellulose assay demonstrated a very small response (absorbance of 0.07 au at a concentration of 10 µM). The difference in the responses of the two assay formats is hypothesized to be caused by the non-specific vs specific immobilization of thrombin onto the substrate. Additionally, both calibration curves had excellent R2 values of 0.97 and 0.98 for the best-fit curves for the cellulose-based assay and the glass-based assay, respectively. The signal between different concentrations eventually became indistinguishable due to the saturation phenomena where all captured aptamers became bound.

Figure 6. Modeling of Copper Reduction Modeling of copper reduction. (a) Copper reduction on detection zone with a 1:2 aptamer to BSA physisorption ratio. Data points are mean absorbance values, and the dashed line is the best-fit curve (four parameter logistic equation). (b) Dependence of tn on iron oxide nanoparticle density captured on the surface, with best-fit curve (exponential decay) as dashed line and best-fit parameters listed in the adjacent table. (c) Experimental kinetic data of copper reduction for various aptamer to BSA physisorption ratios. Data points indicate mean values, error bars indicate one standard deviation. Dashed lines are best-fit curves. (d) Computational modeling results (solid lines) superimposed with experimental data points. The difference (expressed as a normalized objective function) between the model and experiment was 9.2%

Development of Colorimetric Sandwich Aptamer Assay for Thrombin

The aptamer-coated glass microscope slides and DVS-activated cellulose were employed as solid substrates for the immobilization of thrombin as well as the formation of the aptamer sandwich for the colorimetric detection of thrombin. A thrombin calibration curve was constructed for both assay formats using serial dilutions of thrombin in deionized water and measuring the resulting color change using a digital camera in conjunction with Adobe Photoshop. Overall, the analytical capacity of both sensors for the detection of thrombin exceeded expectations with limits of detection of 10 pM (glass-based assay) and 20 pM (cellulose-based assay), while demonstrating a wide detection range (10 pM-200 nM for glass and 20 pM-1 nM for cellulose). Additionally, the glass-based assay demonstrated no response in the presence of 1 x BSA as a negative control and the activated cellulose assay demonstrated a very small response (absorbance of 0.07 au at a concentration of 10 µM). The difference in the responses of the two assay formats is hypothesized to be caused by the non-specific vs specific immobilization of thrombin onto the substrate. Additionally, both calibration curves had excellent R2 values of 0.97 and 0.98 for the best-fit curves for the cellulose-based assay and the glass-based assay, respectively. The signal between different concentrations eventually became indistinguishable due to the saturation phenomena where all captured aptamers became bound.

Figure 7. Thrombin Calibration Curves Calibration curves for thrombin for the glass-based assay. Serial dilutions of thrombin were prepared in deionized water with concentrations ranging between 1 pM and 1 µM. It was found that there was a strong linear response (R2 = 0.99) in the most clinically relevant range of 100 pM to 10 nM; however, after 50 nM the saturation phenomena caused the sensor response to plateau.
Conclusions

In order to meet the urgent demand for a method for the inexpensive, rapid, simple, sensitive, and specific a novel aptamer sandwich assay was developed. The assay consisted of a aptamers physisorbed to a glass microscope slide or DVS-activated cellulose for the immobilization of the target analyte along with a labeling solution of aptamer-iron oxide nanoparticle conjugates and a developing solution of Cu2+. Both sensor formats were highly sensitive with LODs of 10 pM (glass-based) and 20 pM (cellulose-based). When compared to traditional ELISA the sensor has a shorter detection time by a magnitude of 16 times (15 minutes vs 4 hours) and is 60 times less expensive ($0.10 vs $6.00). Future work will focus on incorporating the assay into a microfluidic cassette as well as developing a compact reader to simplify assay operation, multiplexing multiple detection zones onto a single device to detect multiple analytes, further optimizing analytical parameters (catalyst-reduction pair, pH, etc.) to increase sensitivity. It is believed that the developed assays could be a powerful method for the inexpensive, rapid, simple, sensitive, and selective detection of biomolecules for applications ranging from clinical diagnostics and biodefense to environmental monitoring and food safety.

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- Analysis of aptamer-nanoparticle conjugation: Leach et al 2016; Sperling et al 2010
- DVS-activation of cellulose: Yu et al 2012
References


Humor and humor therapy are currently being explored as possible treatments for depression—a disorder with a growing and largely unmet need in modern medicine. According to the Center for Disease Control and Prevention (CDC), “Eleven percent of Americans aged 12 years and over take antidepressant medication” (Pratt). With such prevalence and reliance on antidepressants, it is no surprise that alternative treatments are being explored. But what is the relationship between humor and medicine? Is it possible for the lightness of humor to exist within the highly professional health sphere? If so, what are the effects of humor and can those effects be applied as alternative or supplemental treatments for depression? The first part of this discussion will examine the role of the physician and medical community, as well as the functional benefits humor provides to medical interactions. Then, multiple perspectives regarding humor and humor therapy will be evaluated to consider its application for depression therapy.

**Humor in Context**

The application of humor is not a new idea, and a few institutions have even formally implemented humor practices. For example, the Clown Care Institute was established in 1989 for the Babies and Children’s Hospital at the Columbia-Presbyterian Medical Center (CPMC). This institute introduces clowns to children fighting acute cancer and heart failure to alleviate stress and need for sedation (Balick 2). However, humor therapy does not have to be formal in application. It can exist within the health care system in a variety of ways. Humor therapy, according to the Association of Applied and Therapeutic Humor (AATH), is:

> Any intervention that promotes health and wellness by stimulating a playful discovery, expression or appreciation of the absurdity or incongruity of life’s situations. This intervention may enhance health or be used as a complementary treatment of illness to facilitate healing or coping, whether physical, emotional, cognitive, social or spiritual. (Franzini 2)

Observational studies confirm the presence of humorous dialogue and exchanges in everyday patient-physician interaction. These exchanges can take several different forms. From a simple pun or an exaggeration of fact—nearly anything out of the norm in a hospital environment or therapy session can trigger a humorous response from the patient. Humor can ease anxiety over a diagnosis, or make an intrusive treatment less painful or embarrassing. (DuPre 89). Physicians deal with health, a very personal and very vulnerable part of our existence, and the less anxiety surrounding this interaction, the better and often more effective the treatment. Humor’s relationship with health, both formally and informally, is crucial and very much present.

**Case Study and Functionality**

A closer look at one of these informal humorous interactions reveals the nuance humor adds to the medical setting. “She Laughed”, an excerpt from Patients and Doctors - Life Changing Stories from Primary Care, is a physician’s perspective about delivering a baby and the effects humor has on the delivery. The exchange begins a few weeks before the pregnancy when the expectant mother voices her fears about incorporating traditional Chinese medicines during the pregnancy. She fears her doctor will disapprove of her family’s traditional practices, which among others includes taking a swig of Korean Ginseng just before delivery— or worse yet will not understand the significance of these traditions from her family’s perspective.

> “She wants to bring me all kinds of Chinese medicines, but I know I cannot take those,” Sue said sadly.
> “Do you want to take them?” I asked. Shyly, she nodded.
> “Then why not?” (Borkan 107)

This initial exchange, marked by the doctor’s casual almost nonchalant response, is the opposite of what is expected in a typical medical setting. Her offhand reply functions in two ways. The first gives power back to the patient by being receptive to the role of tradition and the individual’s needs. The doctor ul-
timately knows what will and will not interfere with pregnancy, but instead of belittling the patient with technical jargon, the doctor listens and responds in a manner that is respectful and assures the patient that their perspective is valid. This and other forms of lighthearted or humorous encouragement ensures the patient plays a more informed and responsible role in maintaining their health. (DuPre 129).

The second function of this interaction uses humor to successfully react to a patients non-verbal cues. A study of patient-doctor interactions found that “... physicians who are sensitive to subtle non-verbal cues may be better able to detect and satisfy the social and emotional needs of the patient” (Freidman 55). This exchange appears to confirm this analysis. Aware of sadness in the patient’s speech and her shy, tentative mannerisms, the physician skillfully responds in a way that is reassuring and comforting, rather than confrontational. Patient-doctor interactions often have an unspoken hierarchy (Diogenes 51). The doctor is more knowledgeable and therefore in a greater position of power. By interjecting humor in the form of unexpected and relaxed dialogue, a medical professional can dismantle this hierarchy and communicate with the patient on a personal level.

A few weeks later in the pregnancy, humor is again implemented during a critical moment of delivery. The baby’s head had been crowing for over ten minutes, putting strain on the mother’s perineum. The obstetricians debate among themselves deciding whether to cut an episiotomy to prevent tears. An episiotomy is a procedure that is not usually recommended unless critical for delivery as it can cause infection, incontinence, and other forms of irreversible damage to the mother (“Episiotomy” 1). This is a decision with serious medical consequences and action must be taken in a timely manner. During the delivery, the doctors humorous banter provides stark contrast to this tense situation and produces an environment which aids in the delivery of the child.

“Tch! You will never get [the baby] out without a tear,” Maria Elana stated emphatically while making a sound West Indians use to express disbelief. “Is that a bet?” I asked. “You’re on,” said Maria-Elana. . My patient thought this whole interchange was funny; she started to giggle. Her husband whispered something in her ear. She started to laugh out loud. Somehow that laughter produces the right combination of pressure and relaxation. The baby’s brow began to slip over the edge of the perineum.

Most apparent in this situation is humor’s ability to relax the muscles necessary to deliver the baby. Humor often encourages laughter and other physiological responses (analyzed later in the discussion) that can have a significant impact on the body. But beyond the induced physical effects, there are larger emotional and psychological implications of this exchange. Adopting a lighthearted dialogue under such conditions eases the tension in the room and frames a critical moment of delivery as a routine medical procedure. In fact, this change in tone and situational framing has been recognized as one of the key sociological functions of humor. Even in tense situations and dialogues, the addition of humor can transform the tone of a transaction into one that is more relaxed and conversational (DuPre 97). The doctor is aware of the unique environment dialogue has created and the mention of ginseng in the delivery room only heightens the absurdity. The physicians take their job seriously. However, by exchanging these brief quips they introduce levity and renew confidence in their abilities while simultaneously assuring the patient of her safety and the safety of her unborn child.

Humor is a proven method of “breaking the ice and establishing intimacy” necessary for patient-doctor relations (DuPre97). Childbirth, one of the most intimate medical interactions between a patient and physician, makes the incorporation of humor seem a natural extension of health procedure. What is unique about this interaction is that it involves both the patient and the practitioner engaging in a dance of humorous exchanges. When the tension rose, the doctors reacted gracefully with assuring dialogue and the patient in return laughed and responded positively to the way they handled the delivery. It is not just humor, but the shared experience and reciprocity of humor that makes it such a powerful tool in the medical setting.

But does this intimacy translate to a mental illness like depression? Is humor a power to be harnessed and controlled? Or must it only exist spontaneously
in the ebb and flow of natural conversation to be effective? The implications of its physical and social environmental factors make humor a good candidate for combating depression - a mental illness characterized by both its physical symptoms and its ability to be influenced by social and environmental factors. But to “beli[eve] in the effects of humor is not the same as understanding it” (DuPre 7). And before the relationship between them is analyzed, both humor and depression must be understood in greater detail.

Overview of Depression, Current Treatments, and Challenges

Depression is a chronic condition that affects a large cross section of society, but many cannot afford the cost of treatment throughout their lifetime. A study from the CDC found that “…more than 60% of Americans taking antidepressant medication have taken it for 2 years or longer, with 14% having taken the medication for 10 years or more” (Pratt). The chronic nature of depression can be an economic burden for the individual, but also contributes to high national health care costs. Annually, the U.S. spends over $43 billion dollars on anxiety disorders alone to develop and administer pharmacological treatments (Reinecke 22).

Alternative treatments may be valuable from more than an economic standpoint. This is especially true when alternative therapies have the potential to limit drug dependency, which can be an ongoing struggle for a patient and can cause both emotional and financial distress. In addition to drug dependency there are also severe psychological implications of long term antidepressant use. High rates of insomnia, agitation, anxiety, nervousness and suicidal thoughts and actions have been associated with depressed individuals taking medications in high dosages over prolonged periods of time (Kresser). These debilitating side-effects can often exacerbate the symptoms of depression instead of alleviating them.

In addition, there are significant challenges associated with both the treatment of depression and the implementation of humor therapy. While much research has been dedicated to managing and treating the effects of depression, there is no definitive cure or pathology for the disorder. The origins of depression are thought to be genetic (chemical imbalances within the brain) or to rise from a combination of “psycho-social” environmental factors that contribute to symptoms of depressed mood or loss of interest in normal activities. Depression is also associated with loss of appetite, weight gain or loss, abnormalities in sleep, or suicidal behavior. (Reinecke 22). This wide variety of manifestations makes depression notoriously hard to treat and relapses in the disorder are common, even among those who initially achieved successful remission through drug treatments. Previous research has supported the superiority of drug therapy treatments but new research has reshaped this perception. In fact, Reinecke in Comparative Treatment Series - Depression: A Practitioner’s Guide to Comparative Treatment argues that current research supports “a combination of treatments may be superior to [drug] therapy alone,” and “psychotherapy can achieve results comparable to medication” (38). A possible rationale behind this is that pharmacological therapies do not address the underlying environmental and behavior factors associated with depression. While this opens the door to alternative treatments, it questions whether humor therapy alone can properly address the complexities of depression. On one hand humor is “culturally and situationally reflexive” and can be used in a wide variety of settings among a diverse population (DuPre 192). On the other hand, humor’s wide variety of applications makes it difficult to narrow down a specific treatment that would best meet the needs of patients. However, humor therapy may still be the best means to address the deficits of pharmacological treatments.

Although humor’s versatility makes it difficult to assess treatment options, its specific biological effects have been well documented and well tested. Humor has been linked in multiple studies as a factor that raises pain tolerance for cancer patients and aids in the rehabilitation of heart attack survivors. Significant data from studies include the measurement of increased immune cell activity and production of chemicals in the brain known to counteract the negative effects of stress. (Balick 3). Many of humor’s observed healing phenomena function in the same way as traditional drug therapies, by producing or altering chemical responses in the brain. It is this key physiological response to humor, induced by laughter or a rush of endorphins, that therapists argue should be incorpo-
Humor and the patient becomes more receptive to treatment and less intimidated to ask questions. In a study, it was found overwhelmingly that patients “valued interpersonal over technical skills” among caregivers (DuPre 11). In fact, DuPre asserts that “humor is actually a sophisticated means of organizing and influencing social transaction” and if “humor is inconstant with professionalism; we may want to change our ideas about professionalism” (193). Humor and informal interactions between patient and caregiver are invaluable and maximize the effectiveness of treatment. At times this may require putting the needs of the patient before the doctor’s reputation and usual protocols of the typical health care setting.

Others who oppose humor therapy in application to depression contend that the qualitative nature and experimental design of current studies are flawed. The argument is that it is hard to quantify humor when it is so varied among individuals, and hard to measure results on a large scale. Therefore, very few reflective experiments have been conducted and further research must be done. Often depression studies are subjective to those administering the test, and if subjects self-report their own altered mental state it results in “social desirability contamination” (Bennet 189). This describes that a patient’s desire for a treatment to work leads to a treatment working, and this manifestation of the placebo effect often leads to error and bias. Another issue with humor therapy is the potential to cause harm to the patient. Kubie published a paper in 1971 that vehemently maintained that the use of humor in psychotherapy is destructive for the patient and there was very little room for humor in psychotherapy. (Franzini 2). Humor in severe cases of depression may have belittling effects on the patient, undermine trust or even victimize the patient. Physicians must be wary of the appropriate time to use humor because what often “…makes humor useful [in the medical setting]…leaves little recourse to the person pierced by a humorous barb” (DuPre 187). Also, Bennet deems the positive effects of humor are minimal compared to the possible risk of negative side effects (189). Very few experts completely deny the positive effects of humor, but many caution the public’s overeagerness to incorporate a largely untested, unquantifiable therapy.

**Important Conclusions and Future Applications**

Humor has a complex but undeniable relationship with health that continues to evolve. Humor therapy as a means of mitigating or treating depression, while still in its early stages, shows promise. These therapies have proven to stimulate the brain in a similar and, in some cases, superior manner than traditional medication, with minimal costs and side-effects. With more research, humor therapy and training may eventually have the backing of the scientific community and the
potential to become part of common health practice.

However, even amid these promising results, there are some experts who consider the preliminary results of alternative treatments as insignificant or misrepresented by false data. But however stringent the dissenting ideas about humor therapy, the use of humor as a health communication tool is difficult to refute. Reinecke reasons that the strongest agents of change in psychotherapy are based on the strength of patient-therapist relationships (41). Additionally, if the therapist feels emotionally invested in the patient’s well-being and the patient reciprocates that level of investment through the exchange of humor, this fosters a relationship of mutual aid instead of reliance.

Humor functions as “social footwork” that allows a foundation of trust to be built and thus is crucial to proper diagnosis and patient efficacy (DuPre 83). It can be used as a form of social leveling allowing doctors to communicate with patients from a position of equal power or as subtle recognition of a patient’s non-verbal cues. It can also be used for situational framing to produce levity and establish intimacy when necessary. When used effectively, humor’s diverse functionality can profoundly influence the outcome of critical health procedures and create environments that promote healing and communication. To neglect the establishment of humor as a communication tool or to dismiss it as child’s play would be erroneous as “dissatisfying communication is not only bad medicine, it’s bad science, and it’s bad business...and if [proper communication is used] patients - as well as caregivers - stand to gain” (DuPre 11).

Current professional and scientific positions argue either to reject humor therapy as pseudoscience or use it as a complete replacement for side-effect causing antidepressants. More moderate opinions suggest that a combination of humor therapy and antidepressants may maximize patient benefits. But even these combinations seem impractical or unrealistic to introduce formally. With the immense need for alternative treatments, and humor’s longstanding but understated presence in the health field, the healing power of humor must be officially recognized - but perhaps in a different way than previously proposed by health care professionals.

I propose instead for the shift in attitudes towards the use of humor in the health care environment. This method would allow humor to exist without implementing formal procedure. It does not take up time or additional cost as it calls for a change in mindset not procedure. However, it also allows the positive physiological and environmental effects of humor to permeate into the health sphere and, with luck, patients’ lives as well.

Humor alone does not have the chemical-altering capabilities to counteract severe cases of depression. Formal humor therapy is forced, inorganic and is not as effective as impromptu humor found naturally in many patient-doctor exchanges. Health care providers must instead focus on fostering an environment where humor is celebrated rather than discouraged. An environment where humor is considered necessary, welcome, and not as ineffective or unprofessional. If humor’s functions and applications can be recognized and valued, it can positively impact the lives of those most affected by depression.

References
A major barrier to the success of transplantation is graft rejection, wherein the transplanted tissue is destroyed by the transplant recipient’s immune system. Graft rejection is very common in allografts, in which tissue is transplanted from one individual to another genetically non-identical individual of the same species because the transplant recipient’s white blood cells (immune cells) recognize the donor tissue as “foreign” and attack it. In order to prevent graft rejection, immunosuppressive drugs are administered to suppress the allograft recipient’s immune system. However, immunosuppressive drugs are expensive and they are associated with increased susceptibility to infection, increased risk of malignancy, nephrotoxicity (kidney toxicity), and cardiovascular complications. Furthermore, immunosuppressive drugs do not completely eliminate the problem of graft rejection—for instance, chronic rejection still remains a leading cause of the late loss of renal allografts with a 3-5% annual rate of renal graft loss despite the use of immunosuppressive medication. Hence, immunosuppressive drugs are not the ideal solution to the problem of graft rejection, and another method to achieve and sustain graft survival is desired. Current research aims to discover methods to induce transplant tolerance, in which the transplant patient can sustain the allograft without a need for ongoing immunosuppression. In this paper, two approaches to inducing transplant tolerance, mixed chimerism and regulatory T cell therapy, will be discussed in terms of their potential to solve the major public health problem of safely and effectively sustaining organ transplants.

Transplant tolerance relies on the induction of immune tolerance, a mechanism which prevents autoreactive (self-reactive) immune cells from destroying normal tissue in the individual. In central immune tolerance, autoreactive immune cells, specifically T cells and B cells, are deleted as they mature in primary lymphoid organs (i.e. the thymus and bone marrow). However, some autoreactive immune cells are able to escape this selection process. Peripheral immune tolerance, which occurs in tissue such as lymph nodes where T cells and B cells migrate after maturing, exists as a backup measure to deal with cells that have evaded central tolerance. One mechanism of peripheral tolerance involves the action of regulatory T cells (Tregs). Tregs help suppress the proliferation of autoreactive cells through mechanisms that are not well-characterized. Both central and peripheral immune tolerance act to prevent autoimmunity, and it is hoped that inducing and manipulating these tolerance mechanisms may lead to the discovery of immunotherapy that can induce transplant tolerance.

Mixed chimerism refers to the co-existence of both donor and recipient cells in the host. Transplantation of bone marrow derived cells is often utilized to try to achieve mixed chimerism as a strategy to establish central immune tolerance. The bone marrow transplant can result in the recipient possessing both donor and recipient hematopoietic stem cells in the circulation. The donor hematopoietic stem cells provide a new source of immune cell, which allows the recipient’s immune system to relearn what “self” is, so that the recipient now considers the donor tissue to be self and not foreign. Thus, alloreactive immune cells (i.e. the immune cells that react against the donor tissue) will now be eliminated in the primary lymphoid organs. The success of this concept was first demonstrated in the 1950s by Billingham, Brent, and Medawar. The researchers injected donor cells into the fetuses of a pregnant mouse. Once the mice were born, each one of them was given a skin graft from the donor. Rejection of the skin graft occurred in three of the five mice that were born. The other two mice were able to sustain their skin grafts, even after 77 and 101 days, respectively. This study demonstrated the success of inducing transplant tolerance through the injection of donor cells. They called this phenomenon, “actively acquired tolerance.” This method of inducing transplant tolerance has shown further promising results in murine/rodent models. In one study, mixed chimerism was induced in mice by lethal irra-
diation of recipient mice and reconstitution of these mice with a mixture of host and donor bone marrow.9. The tolerance induced by this technique permitted the long-term acceptance of genetically mismatched skin grafts in mice; these mice were able to fully tolerate grafts from the donor from which they received the bone marrow transplant and exhibited no signs of graft-versus-host disease, where the white blood cells from the donor bone marrow attack the recipient’s body cells.9 Additionally, mixed chimerism has shown promising results in human kidney transplant patients. A study conducted by Scandling et al. at Stanford University followed twelve patients who received a kidney transplant along with enriched donor hematopoietic progenitor cells and T cells.10 A conditioning regimen that included total lymphoid irradiation was used to prevent rejection of the donor immune cells. All patients were given cyclosporine as an immunosuppressive drug and all of them continued taking cyclosporine for at least six months following the renal transplant. In eight of the twelve patients, cyclosporine was discontinued and there was no evidence of graft rejection or graft-versus-host disease. Thus, in this clinical study, the majority of the patients were able to tolerate their kidney transplant following the induction of mixed chimerism.10

However, despite preliminary successful results in the clinic, mixed chimerism does have its shortcomings. Many bone marrow transplant techniques require the use of myeloablative conditioning, in which the recipient bone marrow is ablated via irradiation in order to prevent rejection of the donor hematopoietic cells. The Stanford study described above, for instance, utilized total lymphoid irradiation as part of the protocol for the bone marrow transplants.10 There are many risks associated with myeloablative conditioning, since the host bone marrow is effectively destroyed. As a result, less toxic methods are desired.1,11 One such less toxic method is nonmyeloablative conditioning, which involves the administration of sufficient immunosuppression to permit the bone marrow transplant but the doses are low enough so that adverse effects are avoided.1 Nonmyeloablative conditioning in mixed chimerism has been successful in preliminary studies with humans. In one study by Kawai et al., five transplant patients with end-stage renal disease were given a nonmyeloablative conditioning regimen, and they received an intravenous infusion of donor bone marrow following the kidney transplant. Four of the five patients developed tolerance to the kidney graft and were able to discontinue taking immunosuppressive drugs.12 The success of nonmyeloablative conditioning has also been demonstrated in other studies. In a study by Leventhal et al., eight kidney transplant patients underwent a nonmyeloablative conditioning regimen prior to receiving a graft of bone marrow cells.13 After the kidney transplant, the patients received immunosuppression. Five patients exhibited durable chimerism and were able to tolerate their renal graft; they were taken off all immunosuppressive drugs one year after transplant. Another two patients exhibited transient chimerism and their immunosuppressive drug dosage was reduced. None of those patients produced anti-donor antibodies or exhibited engraftment syndrome or graft-versus-host disease.13 Together, the two clinical studies demonstrate that nonmyeloablative conditioning regimens in bone marrow transplantations can provide a viable and practical means of using mixed chimerism safely in the clinic. Future research should concentrate on refining the protocol for inducing mixed chimerism in the clinic so that a standard protocol, such as one that involves a safe and effective mechanism of inducing stable, long-term chimerism, can be constructed.

Regulatory T cell therapy is another method of inducing transplant tolerance. This method involves the induction of peripheral immune tolerance. Giving donor Tregs to a transplant patient may sustain graft survival as the donor Tregs can prevent the recipient cells from attacking the foreign graft tissue.5 The use of Treg therapy has shown positive results in mouse models. One recent study showed that therapies using donor Tregs prolonged the survival of a human pancreatic islet allograft in a humanized mouse model.14 When human donor Tregs were transferred into mice that contained a functioning human islet graft, only two of thirteen mice rejected the islet graft whereas nearly all the mice that didn’t receive Tregs rejected the graft.14 These results suggest that Treg therapy has the potential to protect a human allograft from rejection. In another study, sublethally irradiated mice were injected with Tregs from the donor. However, when the researchers tried perform-
ing a skin graft with the Tregs, the skin grafts were rejected. The researchers then performed a combination of a bone marrow transplantation and skin engraftment (along with the Treg cell therapy) using skin tissue and bone marrow cells from the same donor. The skin allografts from this experiment showed only minor signs of rejection. Thus, combining Treg cell therapy with mixed chimerism seemed to result in better tolerance of the skin graft. The results of these preliminary mouse studies show that Treg cell therapy can establish better tolerance of allografts.

However, with mixed chimerism, there are complications associated with Treg therapy. As Tregs are not terminally differentiated, they can be reprogrammed to effector T cells. It has been shown that Tregs can lose expression of Foxp3 (a biomarker unique to Tregs), which results in a loss of their immunosuppressive function, or, worse, may result in acquisition of effector T cell capabilities, which could render them capable of destroying host tissue. In addition, almost all research on the usage of T reg cells to induce transplant tolerance have been conducted in animal models. Results in animal models may not translate into the same results in humans. For instance, multiple isoforms of Foxp3 exist in human Treg cells but not in mouse Treg cells, meaning that the immunoregulatory mechanisms of T reg cells may differ between humans and mice. Clinical studies should be conducted to assess the efficacy of Treg cell therapy in humans and more research should be done to acquire a better understanding of Treg cells in general.

At the present, there remains no completely safe and effective solution to inducing transplant tolerance. It will likely take many years before a viable alternative to immunosuppressive medication becomes widely in use. However, the mixed chimerism and the Treg cell therapy approach both show much promise and will hopefully become widely used in clinical settings once all the kinks are worked out. Mixed chimerism, especially, has shown positive results in clinical trials, and scientists have discovered ways to circumvent many of its shortcomings, such as the use of myeloablative conditioning regimens, in recent years. Treg cell therapy has shown positive results in murine models but clinical studies with humans need to be performed to evaluate whether it can be used practically in the clinic. A workable method to induce transplant tolerance could result in a reliable, safer, and potentially cheaper way of receiving grafts. It could also potentially help the organ shortage problem as patients will not need to have another transplant if they fully accept their first graft. Successfully replacing long-term reliance on immunosuppressive drugs with induced transplant tolerance in standard clinical practice will truly be a major milestone in public health and medicine.

References


Abstract

This paper seeks to acknowledge that first and foremost, human health is greatly affected by the environments we live in. Health disparities we observe today are often the product of past discriminatory policies by local governments. Through a case study looking at public transportation investments in the Atlanta Metropolitan Region, I investigate the disparities in public transportation infrastructure investment and differential mortality rates from diseases most likely to be influenced by such disparities. Specifically, I investigate the level of investment of subway lines versus bus lines of the Metropolitan Atlanta Rapid Transit Authority (MARTA). The link between health and the built environment, as evidenced in this case study, points toward a future opportunity for planning departments to work with public health departments to create living spaces that promote health more effectively.

Introduction

The innovations of the automotive industry that brought the car to the masses have also led to sprawling developments throughout the United States. Sprawl is described as the expansion of human populations away from central urban areas into low-density, homogenous, and usually car-dependent communities.

Yet despite our inclinations, humans have a remarkable capacity to plan ahead and shape new environments. These efforts to shape future developments do encounter external influences, such as new innovations and politics, which results in the execution of initiatives that may not be necessary for a region. For example, many of these decisions have led to sprawling developments throughout the nation. Sprawl is a huge problem, especially for equity. For example, because owning an automobile is so necessary for living in sprawling suburbs, those without cars are at a disadvantage because sprawl’s transportation accessibility issues create disparities in accessibility of resources in the community.

This paper focuses more on the disparities of transportation investment and their impacts on health, mainly because recently, a new school of urbanism has emerged within the past 30 years, New Urbanism. Members of this school argue for the importance of “neo-traditional” planning that would reclaim older models of planning - bungalows, set back slightly from the street, for instance, instead of larger totally detached single family homes. Perhaps the most salient focus of the New Urbanists with respect to our focus on the link between transit and health is their support of Transit-Oriented Developments (TODs) to promote economic activity and human health in urban space. These TODs are essentially planned communities linked to a public transportation system. The focuses of the New Urbanists have put addressing urban challenges from a multidisciplinary perspective at the forefront and now, many stakeholders are calling for a stronger push to understand how we can plan for spaces that help promote healthier communities.

If an effective public transportation system is built with well-spaced transit catchment areas, meaning that the distance from any given location to the nearest station will be within a reasonable walking distance, as well as well-lit and safe stations, people will likely be more incentivized to use public transit instead of driving personal vehicles, provided that the benefits outweigh the costs of using public transit. As a result, people are increasingly likely to walk to transit stations and from transit stations to their desired destination. With effective transit investment, we should see improved health outcomes related to increased urban walkability, a hypothesis supported by scientific literature. European and Asian studies have documented significant relationships between greater active commuting or transit use frequency and positive health indicators, including lower body mass index, healthier blood lipid profiles, and lower blood pressure associated with active commuting. Therefore, I hypothesize in locations with fewer public transit investment, we will likely see worse health outcomes.
Background: Health and the Influence of the Built Environment

Figure 1 shows the age-adjusted prevalence of obesity and diagnosed diabetes among U.S. adults aged 18 years or older. Essentially, the redder a state is, the greater the percentage of diagnosed diabetes and obesity is prevalent in that state. Overall, the general trend for both obesity and diabetes is that they are becoming greater national health problems. Obesity prevalence may have been as low as fewer than 14 percent of the population in a given state in 1994 and has now risen to at least 22 percent. Diabetes prevalence used to be as low as less than 4.5 percent and has now risen to at least six percent.

Background II: The Vehicular-Centric Built Environment and Health

The answer to this increase in diabetes and obesity prevalence may lie partially in the history of how the built environment has changed over the past century. The 1956 Federal Highway Act played a key role in the transformation of our urban landscape by setting aside 25 billion dollars to fund construction of 41,000 miles of the Interstate Highway System. As a result of the construction of the highway system, private motor vehicles became the dominant form of transportation. Richard Jackson, one of the nation’s leading experts on the built environment’s relationship with public health, argues that such a relationship exists partly because private motor vehicle transportation made necessary by extensive low-density land use has led to implications for health: people are less active because they walk less, vehicle exhaust degrades air quality, motor vehicle injuries increase, and mental health and social capital are adversely affected. Jackson makes a reference to sprawl through his use of the words, ‘low-density land use.’

Selected health outcomes were based on health outcomes identified by Richard Jackson, who acknowledges a relationship between private motor vehicle transportation and effects on physical activity, respiratory health, and injuries sustained from vehicular accidents. I ended up investigating all diseases of heart and diabetes mellitus.

Background III: Why Atlanta and MARTA’s history

The 50s marked the beginning of business corporations moving to southern and western states to escape higher labor costs in the industrial North and to take advantage of a vast pool of low-wage, non-unionized labor. The combination of Atlanta being a major city in the Sunbelt region that developed in a sprawling pattern as well as a city that experienced significant public transit investment, despite growing reliance on private automobile for transportation, made it my city of interest. MARTA is split between subway and bus transportation formats. MARTA’s subway project was a highly contested development plan during the several years leading up to its passage. In the 1950s, planners desired to implement a new rail system as they believed that grandiose public transportation systems would help boost the growth of Atlanta and its surrounding metropolitan area. A study conducted in 1954 by the Atlanta Region Metropolitan Planning Commission (ARMPC) recommended the construction of a 60-mile, fixed-rail system that would connect city proper with 5 metro area counties: Fulton, DeKalb, Cobb, Gwinnett, and Clayton. Atlanta already had a
bus system in place at that time but the ARMPC argued that buses were a ‘second rate’ means of transportation. The state of Georgia is also interesting in the sense that the original state Constitution did not recognize the legal authority of local governments to provide transportation services. However, due to the proposed amendment obtaining the unqualified support of the newspapers and business community, it passed in 1964 and in 1965, the Metropolitan Atlanta Rapid Transit Authority (MARTA) was created.

After the transit authority was created, MARTA faced several voter referendums before the fixed rail plan was approved. The first referendum which appeared on the ballot in 1968 was voted down by voters in the city of Atlanta and Fulton and DeKalb counties. Key to its defeat was black areas voting against it more than 2-to-1 due to African Americans’ discontent with a lack of adequate rail service planned for the city’s public-housing developments. Throughout the 1970s, MARTA received grants of more than $800 million from the federal government for planning, design, land acquisition and construction of a rapid rail system. The bond referendum went to the ballot again in 1971 and this time it passed in three of the five jurisdictions: the city, Fulton County, and DeKalb County. Key to its passage was a last minute decision to heed the warnings of black political leaders and an agreement to satisfy 90 percent of the black political agenda by substituting a rail line for the proposed busway to the Perry Homes community, endorsing minority contracting, and committing to maintaining a fifteen-cent fare for seven years. As a result, construction began and even though, sadly, many of the promises to the African Americans were not kept, the rail system was built and the first train began operating on June 30, 1979.

Methods

Selection of site

The Atlanta metropolitan region was selected as the case-study region. A city located in the Sunbelt region of the United States was chosen because these Sunbelt cities are often newer and created after the invention of the automobile and around the time of the passage of the Federal Highway Act of 1956, which led to construction of an enormous amount of interstate freeways in the United States. As automobiles began to dominate the transportation scene of the United States, people have been left with little or no opportunities to walk or cycle for transportation, which may partially explain the shift in American health outcomes, such as the rise in obesity rates. Research has indicated that between 1980 and 2002, obesity prevalence in the United States doubled in adults aged 20 years or older and overweight prevalence has tripled in children and adolescents aged 6 to 19 years.

Counties in the Atlanta metropolitan region were selected for analysis based on the African-American population in the county, as well as total population for each county. To address demographics differences, I looked for two counties in the Atlanta metropolitan area that had similar demographics prior to the construction of MARTA. Two counties of similar demographics prior to the construction of MARTA with significant MARTA stations were DeKalb and Fulton County. I looked at percentages of minorities in DeKalb versus Fulton County and found that in 1980, both DeKalb and Clayton counties had a population of mostly caucasians. Clayton County had a population of 91.4 percent white and 7.6 percent black. DeKalb County had a white versus black split of 71.3 percent and 27.5 percent, respectively. By selecting these counties versus other counties, I tried to control for potential effects of counterurbanization which, in this case, would be the flight of whites away from areas that experienced growth in the African American population.

Obtaining Health Indicators Information:

After establishing the two counties for our retrospective analysis: Clayton County and DeKalb County, I compared health outcomes between the two counties by using the US Census Bureau’s vital statistics, specifically using mortality statistics categorized by cause of death and county. In order to identify any correlations, I compared data from the most recent vital statistics with vital statistics from 1980. To further strengthen my correlations, I also made sure to identify correlations between physical activity and potentially related health conditions such as obesity and also attempted to track down data comparing population growth between the two counties and ridership levels.

Hypothesis

We identified Clayton County as the county without significant hard-rail MARTA investment and DeKalb
County as the county with significant MARTA investment. Thus, if my hypothesis that counties without significant hard-rail (subway) MARTA investment will have worse long-term health outcomes is correct, we should see the percent change of mortality based on a few causes of death related to public transit investment to worsen progressively in Clayton County and either no change or improvement in DeKalb County.

Analysis

I successfully obtained the necessary information on mortality from the years 1980 through 1993 using the US Census Vital Statistics. The key causes of mortality I used in my analysis were diabetes mellitus and diseases of the heart. Diseases of the heart was a comprehensive grouping of major cardiovascular diseases, rheumatic heart disease, hypertensive heart disease, ischemic heart disease, and a category called ‘other heart diseases.’ I compiled my data together for mortality from diseases of the heart and diabetes mellitus into the tables (Figure 2) below:

<table>
<thead>
<tr>
<th>Disease of Heart</th>
<th>Clayton County</th>
<th>DeKalb County</th>
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<tr>
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<td>1990</td>
<td>1054</td>
<td>1016</td>
</tr>
</tbody>
</table>

Figure 2. Vital Statistics Data on Mortality from Diseases of Heart and Diabetes

Figure 3 shows mortality from diabetes mellitus in Clayton County and DeKalb County, specifically indicating that more people are dying in DeKalb County than in Clayton County, as highlighted by the seemingly steeper red curve. Figure 4 shows mortality from diseases of heart in Clayton County and DeKalb County, with both counties seem to see a stable number of people dying from diseases of heart. To provide a more robust analysis of the trends, percent change was calculated at the five-year level from 1980 to 1985 as well as the percent change from 1980 to 1993. Based on the above percentage change calculations, we observe that there are greater percentage changes in Clayton

Figure 3 and Figure 4.
County for both mortality causes over both the 5 year and the 13 year periods than in DeKalb County. Tracking down correlations between population growth in the two counties and ridership totals would help make any argument for a correlation between transit investment and health outcomes in my two counties more robust. According to population statistics from the United States Census, the population for Clayton County in 1980 was 150357 people and 182052 people in 1990. DeKalb County had a population of 483024 people in 1980 and 545837 in 1990. When we calculate the percent change in population, we get growth of 21 percent in Clayton County and 13 percent in DeKalb County. While I was unable to obtain ridership statistics on a county level, I did obtain overall ridership data in the form of a graph depicting transit ridership trends in Atlanta (MARTA) measured in linked passenger trips which is defined as a trip from origin to destination on the transit system (see Figure 5 below). Even if a passenger must make several transfers during a one-way journey, the trip is counted as one linked trip on the system. Unlinked passenger trips count each boarding as a separate trip regardless of transfers. Not having the unlinked passenger trip data likely does not affect our analysis; however, the data would be useful in identifying if the amount of transfers needed to make a trip is a potential reason for any decrease in public transit ridership. Overall, rail ridership has grown from 10,000,000 linked passenger trips in 1980 to around 25,000,000 linked passenger trips in 1993. Bus linked passenger trips has fallen from 65,000,000 to 40,000,000 from 1980 to 1993. That translates to a 150 percent growth for rail ridership and a shrinkage of 38.5 percent for bus ridership. Total ridership has changed from 75,000,000 linked passenger trips in 1980 to 65,000,000 in 1993, which is a decrease of 13.3 percent. Population growth is similar in both counties but we observe an overall decrease in total transit ridership.

**Conclusion**

Based on our analysis, while diabetes and diseases of heart have seen greater percent changes in mortality from 1980 to 1993 in Clayton County than DeKalb County, this may potentially be confounded by population growth. There may still be evidence of a correlation between transit investment and health outcomes due to population growth not being tremendously substantial: 21 percent in Clayton County and 13 percent in DeKalb County. Yet, even though population may have grown by a little, MARTA ridership across Atlanta has dropped by a little. It is possible that decreased ridership means that people are driving private cars more often and consequently, their health outcomes may have suffered due to increased adoption of private transport. As much of the existing literature on the built environment and health concludes, there needs to be further robust studies examining the relationship between built environment investments and health outcomes to produce stronger correlations.

**Challenges and Future Directions**

I outlined some of the challenges involved with this project earlier in my methodology and analysis sections. First, it was difficult to locate incidence data on health conditions before the current decade so I had to resort to using vital statistics on mortality instead. The populations involved in the mortality statistics are of an advanced age so it was not an ideal arrangement. One such future direction could be to obtain data on incidence rates for a specific age-group in order to avoid the skewed datasets I had to work with. Second of all, there are no standardized built environment indicators so I had to pool together the limited literature on the relationship between the built environment and health to make inferences about the health outcomes that would be affected by transportation investment. In my analysis section, I detailed the difficulty of locating ridership statistics by county in the limited time I had to write this paper. It may also be possible that the MARTA county offices no longer have the data on file. Finally, I will also add that interdisciplinary investigations are difficult because there are so many possible confounds and interactions that could play a role in these relationships. It should be noted that there needs to be further investigations of correlations between health outcomes and ethnic background and careful consideration of potential confounds, such as socioeconomic status and consequent factors such as diet and stress, if future studies are to be conducted.
References


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